ISSN (P) : 2589-9120 / (O) : 2589-9139
PubMed-National Library of Medicine - ID: 101773527

International Journal of Medical Science and Applied Research (IJMSAR)

Available Online at: https://www.ijmsar.com

Volume – 4, Issue – 5, September – 2021, Page No. : 01 – 10

Review Article on Acromesomelic Dysplasia

[1]Dr. Shanet Susan Alex, Doctor of Pharmacy Graduate, Nazareth College of Pharmacy, Othera, Thiruvalla, Kerala, India

[2]Dr. Keerthana Kripa R R, Doctor of Pharmacy Graduate, Nazareth College of Pharmacy, Othera, Thiruvalla, Kerala, India

[3]Dr. Sruthy Merry Sam, Doctor of Pharmacy Graduate, Nazareth College of Pharmacy, Othera, Thiruvalla, Kerala, India

Citation of this Article: Dr. Shanet Susan Alex, Dr. Keerthana Kripa R R, Dr. Sruthy Merry Sam "Review Article on Acromesomelic Dysplasia,'' IJMSAR – August – 2021, Vol. – 4, Issue - 5, P. No. 01-10.

Corresponding Author: Dr. Shanet Susan Alex, Doctor of Pharmacy Graduate, Nazareth College of Pharmacy, Othera, Thiruvalla, Kerala, India

Type of Publication: A Review Article

Conflicts of Interest: Nil

Abstract

Acromesomelic dysplasia is an exceptionally rare, inherited, progressive skeletal disorder that leads to a specific sort of short stature referred to as short-limb dwarfism. Also known as Acromesomelic dwarfism. It affects distal and middle segments of the extremities. It occurs in syndromic and non-syndromic forms. In syndromic forms, it shows association with cardiac, respiratory, neurological and genital abnormalities. The disorder is distinguished by acromelia and mesomelia. The extremely short hands, fingers, feet, and toes are characteristic. The intelligence is normal. These findings are apparent during the primary years of life. Acromesomelic dysplasia segregates in autosomal recessive mode with close association with genetics and offspring of direct blood relation parents. There's no cure for this condition. The available treatments aim at improving the standard of life.

Keywords

Acromesomelic dysplasia, short, mutations, dwarfism, recessive, rare, gene, coding, AMD, skeletal, disorder.

Acknowledgement

I would like to express my deep gratitude towards my teachers, family and friends for their support and guidance.

Introduction

Acromesomelic dysplasia (AMD) or Acromesomelic dwarfism is a rare group of autosomal recessive form of skeletal disorders characterized by dwarfism associated with anomalies ofmiddle and distal segments of the extremities i.e., limb shortening. AMD occurs in non-syndromic and syndromic forms. In the syndromic form, it's related to respiratory, genital, cardiac and neurological abnormalities. Two characteristic features are mesomelia and acromelia. Mesomelia is the shortening of the bones of the forearms and lower limbs relative to the upper parts of these limbs. Acromelia is associated with the shortening of extremities affecting primarily hands and feet. Therefore, the short stature of affected individuals is the results of unusually short forearms and abnormal shortening of bones of the lower limbs. They are visible from the first years of life itself. GDF5, NPR2, BMPR1B gene mutations are associated with AMD. Natriuretic peptide receptor B (NPR-B) is expressed in several tissues, including cells inside the growth plates of growing bones. They are trigerred by a small protein called CNP and that in turn activates other proteins including cyclic GMP dependent protein kinase 2. NPR-B appears to be important for regulating the complex process of cell multiplication and differentiation during skeletal growth. Those individuals who doesn't have working copies of NPR-B have AMDM, while individuals who carry one non-working copy of NPR-B tend to be shorter than non-carriers.

Endochondral bone growth occurs at growth plates within the axial and appendicular skeleton. Chondrocytes proliferate, differentiate, increase in size, synthesize, calcify matrix, and become apoptotic, ultimately resulting in the recruitment of osteoblasts that replace the calcified cartilage matrix with bone. Endochondral growth is mediated by endocrine, paracrine, and autocrine factors many of them are identified through the study of individuals who have abnormal growth patterns. Present review discusses about the types, presenting features, genetics, etiology, diagnosis and emerging treatments of acromesomelic dysplasia. [1,3,4,11]

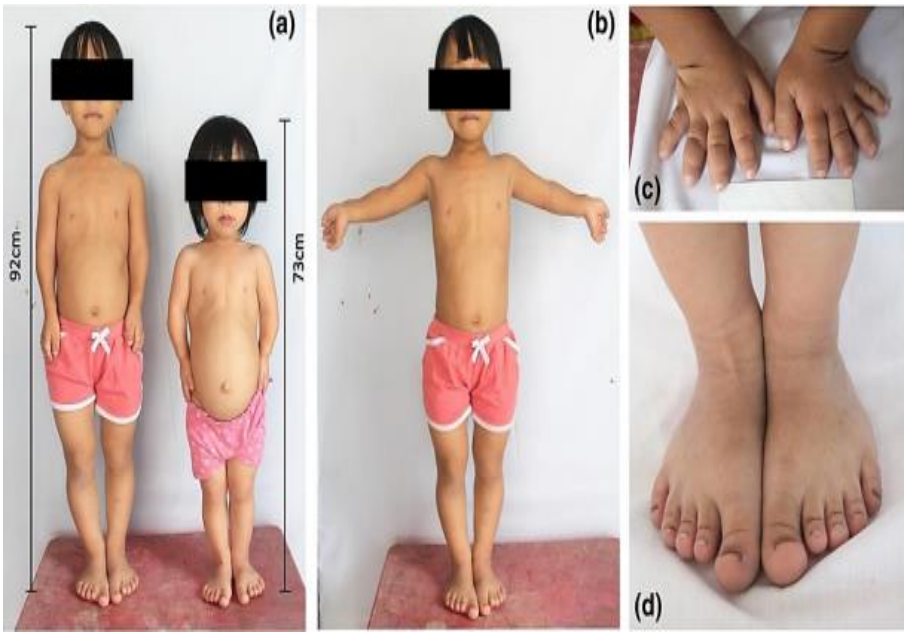


Figure 1: Represents images of 8 and 4yr old siblings with AMD from Vietnam TYPES

1. Acromesomelic Dysplasia, Maroteaux Type (AMDM)
2. Acromesomelic Dysplasia, Osebold-Remondini Type
3. Acromesomelic Dysplasia with Genital Anomalies, Demirhan Type (AMDD)
4. Fibular Hypoplasia and Complex Brachydactyly (Du Pan Syndrome)
5. Acromesomelic Dysplasia Grebe Type (Including Hunter-Thompson Type)

AMDM, characterized by severe dwarfism (height below 120 cm), limbs and vertebral shortening, results from mutations in the gene natriuretic peptide receptor-2 (NPR2). Birth lengths and weights are normal, even though mild shortening of long bones may be detected in some affected infants by clinical and radiographic examination.

The Osebold-Remondini syndrome is a bone dysplasia which is characterized by mesomelic short limbs and short stature, absence or hypoplasia of second phalanges with synostosis of the remaining phalanges, carpal and tarsal coalitions, and no other anomalies.

AMDD type also referred to as chondrodysplasia acromesomelic, with or without genital anomalies and is characterized by short stature, very short limbs and hand or foot malformations. The severity of limb abnormalities rises from proximal to distal with profoundly affected hands and feet showing brachydactyly or rudimentary fingers. An important gene associated with AMDD is BMPR1B. Affiliated tissues include uterus, bone and amygdala, and related phenotypes are primary amenorrhea and short toe.

The major features of Du Pan Syndrome are as follows the axial skeleton is normal and short stature is due to symmetric limb malformations. Association of the fingers has varied between patients, but the thumbs are button-like and radially deviated. The metacarpals are shortened to differing degrees; the first metacarpals may be shortened considerably. The phalangeal bones are short, particularly the middle ones, which may even be absent in some of the fingers in certain cases.

Acromesomelic Dysplasia Grebe Type (AMDG) is defined by severe dwarfism at birth, severe shortening and abnormalities of limbs and long bones. It was localized to chromosome 20q11.22 and GDF5 gene. Acromesomelic Dysplasia Hunter Thompson type (AMDH) is also associated with severe dwarfism, lower limbs more affected than upper limbs and large joint dislocations. It was also mapped to chromosome 20q11.22 and large duplications in the coding segment of GDF5 gene. AMDG and AMDH have normal vertebral bones.1,4,7,10

Clinical Features

AMD is characterised by the inhibition of growth of certain long bones. Affected individuals usually have short forearms, lower legs and short stature. These findings are apparent from the first years of life. Abnormal bone and cartilage development is also a feature.

Infants usually have a normal birth weight. In addition to having unusually short, broad hands and feet, affected infants may also have characteristic facial abnormalities that are apparent at birth. This includes macrocephaly, frontal bossing, occipital prominence, a slightly flattened midface or pug nose.

In the first year of life, as the forearms, lower legs, hands, and feet do not grow proportionally with the rest of the body, short-limbed dwarfism begins to become evident. Due to abnormal ossification of bones of arms the ulna, radius may be markedly shortened or

curved. In addition, end portion of radius may be completely or partially dislocated. This is known as Madelung deformity. Affected individuals may be unable to fully extend their arms, rotate the arms so the palms face down or rotate their arms so the palms face upward. Some of them will also experience osteoarthritis.

During the second year of life, the epiphyses may begin to appear as abnormally shaped cone or a square and may fuse prematurely. Thus, the fingers and toes appear short and stubby i.e., brachydactyly; the hands and feet may seem unusually short, broad, and square; and the feet may seem abnormally flat. In large number of individuals, the great toes may appear relatively large in contrast to the other toes. Also, the finger and toenails may also appear abnormally short and broad, though they are otherwise normal. In early childhood, extra, loose skin may develop over the fingers.

Then during the early childhood AMD patients may also have abnormalities of bones of vertebrae. Experience progressive and abnormal curvature of spine. Include kyphosis and lumbar hyperlordosis.

In rare cases, additional abnormalities may be present including, delayed puberty and corneal clouding.5,8

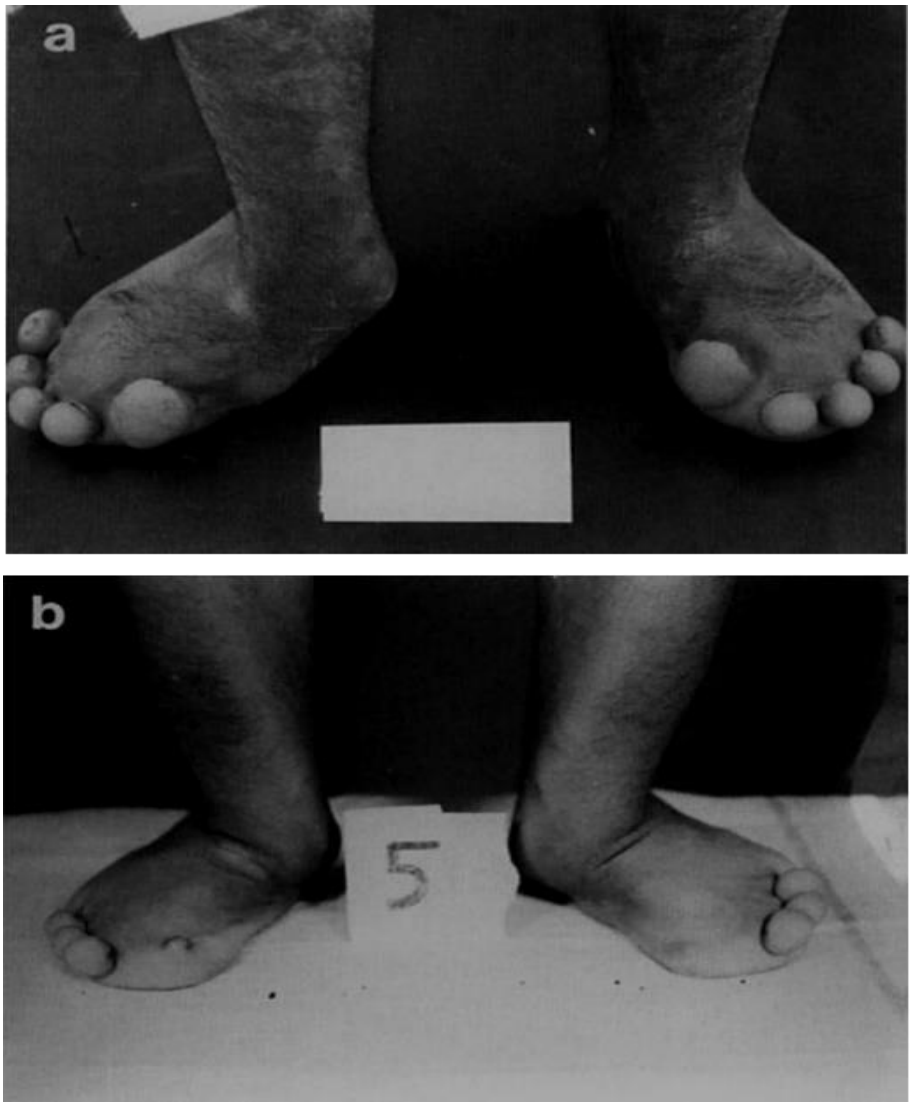


Figure 2: Feet fixed in equinovalgus position

Etiology

In the nucleus of human cells there is chromosomes, which carry the genetic information for each individual. Human body cells normally consist of 46 chromosomes. Human chromosomes are paired and are numbered from 1 to 22 and the sex chromosomes are designated as X and Y. Males have one X and Y chromosome each and females have two X chromosomes. Each chromosome has a short arm named as "p" and a long arm named as "q". Chromosomes are further sub-divided into many bands and are numbered. These numbered bands designate the location of the thousands of genes that are present on each chromosome.

Genetic diseases are governed by the combination of genes for a particular trait that are on the chromosomes received from the father and the mother.

Recessive genetic disorders happens when an individual gets two copies of an abnormal gene for the same trait, one from each parent. If an individual receives one normal gene and one gene for the disease, the person will become a carrier for the disease but usually will not show any symptoms. The risk to have a child who is a carrier like the parents is 50% with each pregnancy. The risk for two carrier parents to both pass the defective gene and have an affected child is 25% with each pregnancy. The chance for a child to receive normal genes from both parents and be genetically normal for that particular trait is 25%. The risk is the same for both genders.

Dominant genetic disorders take place when only a single copy of an abnormal gene is necessary to cause a specific disease. The abnormal gene can be inherited from either the father or mother or can be the result of a new mutation or gene change in the affected person. The risk of passing the abnormal gene from affected parent to offspring is 50% for each pregnancy. The risk is the same for both genders. So, family history and being a child born to parents who are close blood relatives are important risk factors for AMD.

Dominant genetic disorders take place when only a single copy of an abnormal gene is necessary to cause a specific disease. The abnormal gene can be inherited from either the father or mother or can be the result of a new mutation or gene change in the affected person. The risk of passing the abnormal gene from affected parent to offspring is 50% for each pregnancy. The risk is the same for both genders. So, family history and being a child born to parents who are close blood relatives are important risk factors for AMD.

Acromesomelic dysplasia (AMD) are a group of rare autosomal recessive form of skeletal disorders. AMDM has been traced to chromosome 9 at gene map locus 9p13-12. Genetic studies shows that the mutation at chromosome 9p13-12 is in a gene that codes for a protein the affects bone development, natriuretic peptide receptor B (NPR-B). This is a receptor for hormone C-type natriuretic peptide, a hormone that is very important for bone growth. They have all skeletal elements, but have abnormal rates of linear growth. AMDM have a prevalence of ~1/1,000,000.

Osebold-Remondini type, which appears to be autosomal dominant. It has not been genetically mapped yet.

Acromesomelic dysplasia with genital anomalies (AMDD) maps to 4q23-24. The gene found at chromosome 4q23-24 codes for a protein known as bone morphogenetic protein receptor, type 1B (BMPR1B). This is a receptor for GDF5.

AMDG and Du Pan syndrome have been mapped to chromosome 20 at gene map locus 20q11.2.

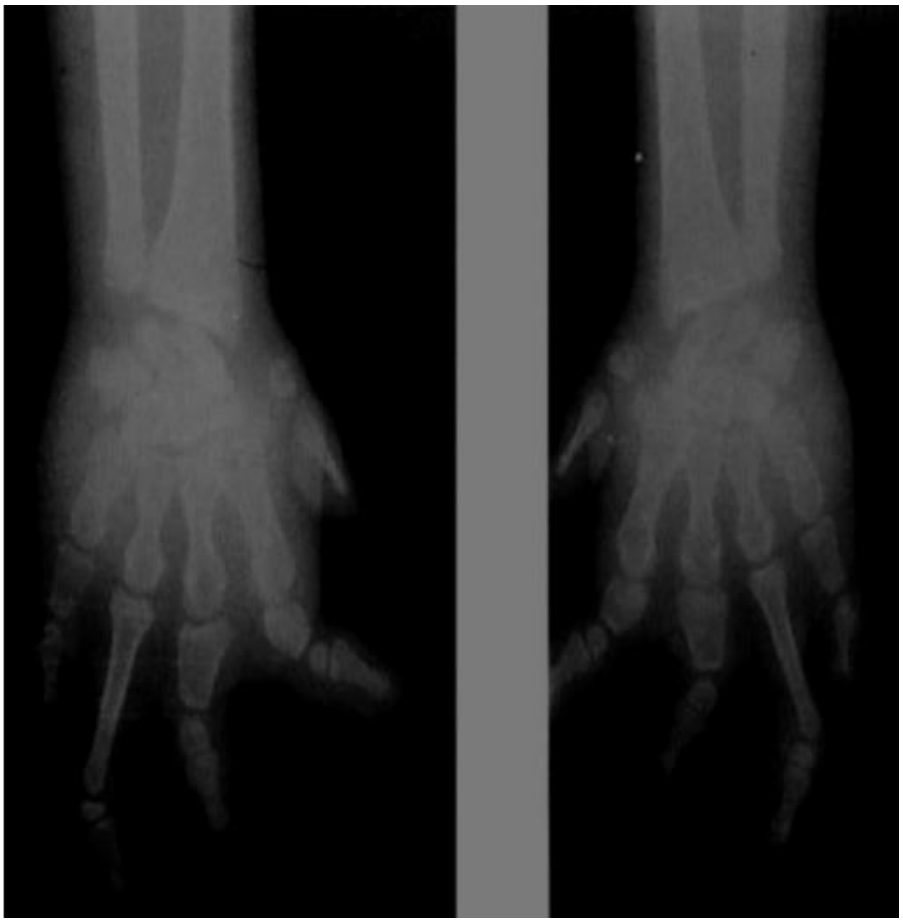
The gene located at chromosome 20q11.2 codes for a protein known as growth and development factor-5, GDF5, previously named cartilage-derived morphogenetic protein-1, CDMP1. 1,2,5,8,9,15

Diagnosis

Usually, AMD is diagnosed during the first years of life. For the diagnosis we use a combination of clinical evaluation (ex., anthropometrics), detailed patient history, identification of characteristic findings, advanced imaging techniques and differential diagnosis. Although the hands and feet may appear unusually short and broad at birth, the progressive abnormalities associated with the disorder typically do not become apparent until late infancy or early childhood.

Specialized x-ray studies may confirm the abnormal development and premature fusion of the regions where the diaphyses of bones of the arms and legs meet their epiphyses. Along with that they may disclose the abnormal fusion of the epiphyses within the phalanges, metacarpals, metatarsals. These types of studies may also confirm the presence or degree of resulting bone abnormalities as well as other skeletal abnormalities that may be associated with acromesomelic.

Molecular genetic testing/ genotyping is also used in diagnosing rare hereditable disease affecting skeletal abnormalities.8,1



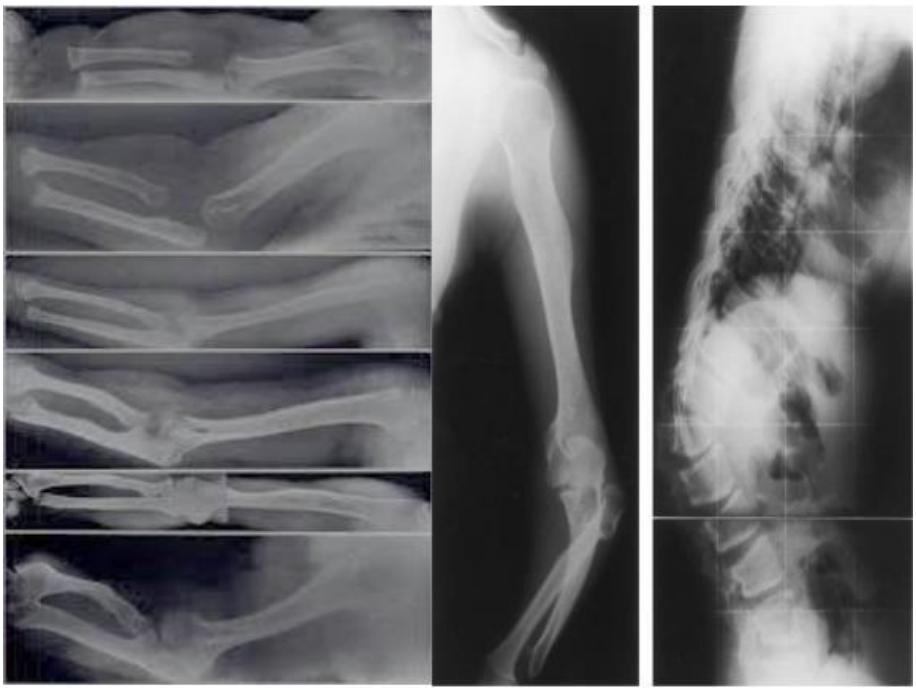


Figure 3: Shows some x-ray of AMD

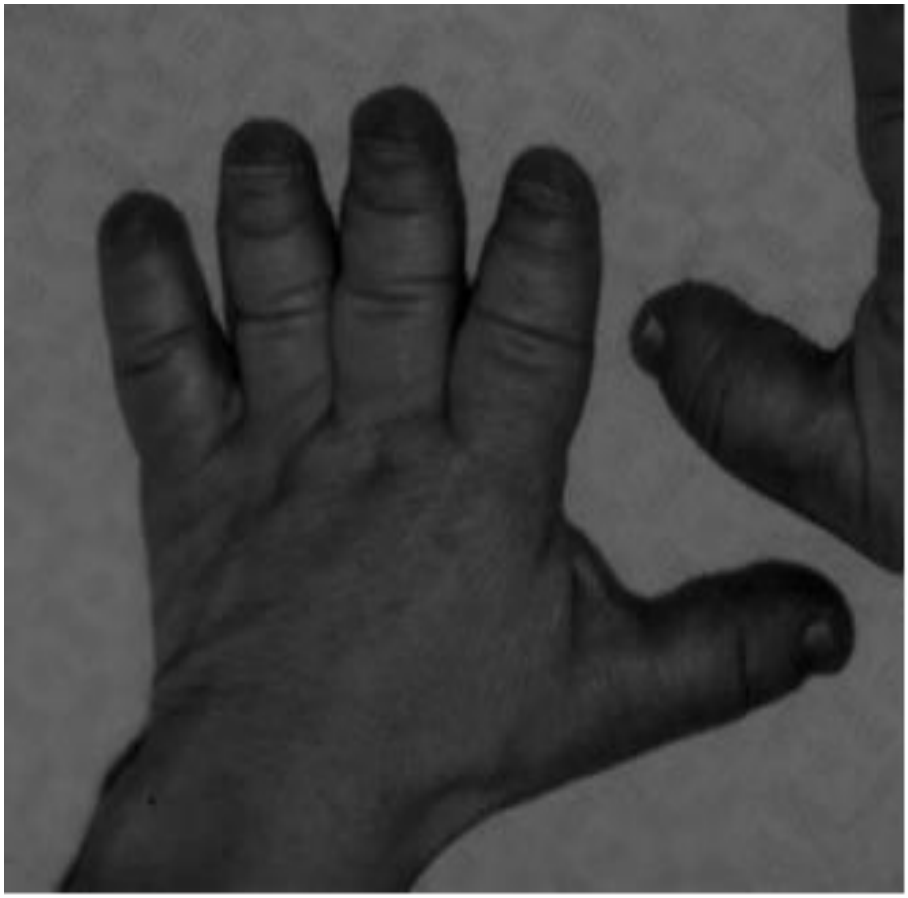


Figure 4: Broad fingers with redundant skin

Therapeutic Management

There's no prevention to AMD. The treatment of AMD is targeted towards specific symptoms and physical characteristics that is found in a particular patient. For the treatment a coordinated team of specialists is required. This include pediatricians, orthopedics, physiotherapists and other specialists. The patients will have a normal life expectancy.

The treatment is usually supportive and symptomatic. For example, abnormal curvature of spine is treated by a combination of exercises, physiotherapy, other supportive techniques like braces, casts, and in severe cases, corrective surgery.

Genetic counselling is recommended for affected individuals and their families. Early intervention is important to ensure that children with AMD to reach their potential. Special services that may be beneficial to affected children include social support, other medical, social support or vocational services.

For the treatment of associated kyphosis pain killers and osteoporosis medications are used. Lumbar hyper lordosis therapy consists of physiotherapy and braces. Also, treatment for coexisting depression and anxiety should also need to be emphazised. 1,12 Investigational Therapy

Recombinant human growth hormone (rhGH) has been employed in a few number of patients with AMDM and none showed an improvement in height velocity. Hence, rhGH is not proposed for treatment of these disorders. But there are other studies with rhGH in AMD showing that it will improve height by a few centimeters if treated long term. Although it will not cure the disease. Side effects associated with GH therapy are nerve pain, edema, carpel tunnel syndrome, risk of DM/ DLP etc.

By using 39 amino acid CNP analog/BMN111, it was observed that this CNP analog inhibits fibroblast growth- factor-mediated MAPK activation. Notable recovery of axial and appendicular skeleton lengths, and improvements in dwarfism-related clinical features including skull flattening, reduced crossbite, straightening of the tibias and femurs was observed by treating mice with this analog.

In a newer study showed that pharmacological inhibitor of MEK/ERK pathway might improve bone growth. 1,12,13

Conclusion

Acromesomelic dysplasia are a group of rare skeletal disorders leading to severe dwarfism and abnormal skeletal morphology. Treatment of AMD includes physiotherapy, using braces and casts, corrective surgery, therapy for associated kyphosis, lumbar hyperlordosis, anxiety, depression. It is related to family history and being born to parents who are close blood relatives. AMD is not curable and the therapy aims at improving the quality of life.

According to a case report AMD is associated with GH resistance, which when overcome by high dose of GH there's improvement in height during childhood and adulthood and quality of life. As well as insulin-like growth factor 1 are also indicated in showing positive results. The results may vary per person.

CNP administration could rescue the skeletal phenotype in AMD. Preclinical studies have shown promising findings in mouse models, with a correction of the dwarfism phenotype. In a multinational including 35 children administering vosoritide at a dose of 15 µg/kg demonstrated a sustained increase in the annualized growth velocity. Long term studies with vosoritide are ongoing.

Effect of pharmacological inhibitor of MEK/ ERK pathway has only been studied in mice. So, further studies are needed to analyse its effectiveness in humas. There's a need of more advanced studies and researches for the management and treatment of this disorder. 4,8,12,13

References

1. Khan, S., Basit, S., Khan, M., Muhammad, N., & Ahmad, W. (2016). Genetics of human isolated acromesomelic dysplasia. European Journal of Medical Genetics, 59(4), 198-203. doi: 10.1016/j.ejmg.2016.02.011
2. Olney, R., Bükülmez, H., Bartels, C., Prickett, T., Espiner, E., Potter, L., & Warman, M. (2006). Heterozygous Mutations in Natriuretic Peptide Receptor-B (NPR2) Are Associated 11 with Short Stature. The Journal of Clinical Endocrinology & Metabolism, 91(4), 1229- 1232. doi: 10.1210/jc.2005-1949
3. Potter, L., Abbey-Hosch, S., & Dickey, D. (2005). Natriuretic Peptides, Their Receptors, and Cyclic Guanosine Monophosphate-Dependent Signaling Functions. Endocrine Reviews, 27(1), 47-72. doi: 10.1210/er.2005-0014
4. Bartels, C., Bükülmez, H., Padayatti, P., Rhee, D., van Ravenswaaij-Arts, C., & Pauli, R. et al. (2004). Mutations in the Transmembrane Natriuretic Peptide Receptor NPR-B Impair Skeletal Growth and Cause Acromesomelic Dysplasia, Type Maroteaux. The American Journal of Human Genetics, 75(1), 27-34. doi: 10.1086/422013
5. Al-Yahyaee, S., Al-Kindi, M., Habbal, O., & Kumar, D. (2003). Clinical and molecular analysis of Grebe acromesomelic dysplasia in an Omani family. American Journal of Medical Genetics, 121A (1), 9-14. doi: 10.1002/ajmg.a.20256
6. Hume, A., Buttgereit, J., Al-Awadhi, A., Al-Suwaidi, S., John, A., & Bader, M. et al. (2008). Defective cellular trafficking of missense NPR-B mutants is the major mechanism underlying acromesomelic dysplasia-type Maroteaux. Human Molecular Genetics, 18(2), 267-277. doi: 10.1093/hmg/ddn354
7. Khan, S., Ali, R., Abbasi, S., Nawaz, M., Muhammad, N., & Ahmad, W. (2012). Novel mutations in natriuretic peptide receptor-2 gene underlie acromesomelic dysplasia, type maroteaux. BMC Medical Genetics, 13(1). doi: 10.1186/1471-2350-13-44
8. Tran, T., Cao, M., Luong, L., Le, P., Vu, D., & Ta, T. et al. (2019). Acromesomelic dysplasia Maroteaux-type in patients from Vietnam. American Journal of Medical Genetics Part A. doi: 10.1002/ajmg.a.61192
9. Kant, S., Polinkovsky, A., Mundlos, S., Zabel, B., Thomeer, R., & Zonderland, H. et al. (1998). Acromesomelic Dysplasia Maroteaux Type Maps to Human Chromosome 9. The American Journal of Human Genetics, 63(1), 155-162. doi: 10.1086/301917
10. Ahmad, M., Abbas, H., Wahab, A., & Haque, S. (1990). Fibular hypoplasia and complex brachydactyly (Du Pan Syndrome) in inbred Pakistani kindred. American Journal of Medical Genetics, 36(3), 292-296. doi: 10.1002/ajmg.1320360309
11. Arya, V., Raj, M., Younes, M., Chapman, S., Irving, M., Kapoor, R., & Buchanan, C. (2020). Acromesomelic Dysplasia, Type Maroteaux: Impact of Long-Term (8 Years) 12 High-Dose Growth Hormone Treatment on Growth Velocity and Final Height in 2 Siblings. Hormone Research

in Paediatrics, 93(5), 335-342. doi: 10.1159/000511874

12. Marzin, P., & Cormier-Daire, V. (2020). New perspectives on the treatment of skeletal dysplasia. Therapeutic Advances in Endocrinology and Metabolism, 11, 204201882090401. doi: 10.1177/2042018820904016
13. Geister, K., Brinkmeier, M., Hsieh, M., Faust, S., Karolyi, I., & Perosky, J. et al. (2012). A novel loss-of-function mutation in Npr2 clarifies primary role in female reproduction and reveals a potential therapy for acromesomelic dysplasia, Maroteaux type. Human Molecular Genetics, 22(2), 345-357. doi: 10.1093/hmg/dds432
14. Langer, L., Beals, R., Solomon, I., Bard, P., Bard, L., & Rissman, E. et al. (1977). Acromesomelic dwarfism: Manifestations in childhood. American Journal of Medical Genetics, 1(1), 87-100. doi: 10.1002/ajmg.1320010110
15. Jackson, M., Marks, L., May, G., & Wilson, J. (2018). The genetic basis of disease. Essays In Biochemistry, 62(5), 643-723. doi: 10.1042/ebc20170053

Abbreviations

MEK MAPK	Mitogen activated protein kinase
ERK	Extracellular signal regulated kinase
AMDM	Acromesomelic Dysplasia, Maroteaux Type
AMDD	Acromesomelic dysplasia with genital anomalies
AMDG	Acromesomelic Dysplasia Grebe Type
AMDH	Acromesomelic Dysplasia Hunter Thompson type
CNP C	C-type natriuretic peptide
GH	Growth hormone
RhGH	Recombinant human growth hormone
DM	Diabetes mellitus
DLP	Dyslipidemia
CDMP	Cartilage derived morphogenetic protein-1
GDF5	Growth and development factor
BMN	Vosoritide
NPR B NPR 2	Natriuretic peptide receptor B
BMPR1B	Bone morphogenetic protein receptor type 1B
GMP	Guanosine monophosphate