Myhre syndrome

Myhre syndrome is a condition involving short stature, characteristic facial features, hearing loss, limited joint mobility, a buildup of scar tissue (fibrosis) in the skin and internal organs, and other problems affecting multiple body systems. Affected individuals often have problems with the heart and blood vessels (cardiovascular system), the lungs and airways (respiratory system), and the skeletal system. The cardiovascular and respiratory problems gradually get worse and can lead to potentially life-threatening complications. Cancer also occasionally occurs in Myhre syndrome.

People with Myhre syndrome usually have delayed development of language and motor skills such as crawling and walking. Although intelligence can be normal in affected individuals, most have intellectual disability that ranges from mild to moderate. Some people with this disorder have behavioral issues such as features of autism spectrum disorder affecting communication and social interaction. Hearing loss occurs in most people with Myhre syndrome, usually beginning in early childhood and gradually worsening; this hearing loss may not be detected promptly and can contribute to learning and behavioral problems.

Fibrosis in Myhre syndrome can occur spontaneously or develop following surgery or trauma. Affected individuals typically have stiff, thickened skin; this skin condition may not be noticeable during infancy, but worsens over time. Usually the skin changes first appear on the palms of the hands, the soles of the feet, the back of the elbows, and the front of the knees. Eventually the skin thickens on other parts of the body. As a result of the thicker skin, affected individuals typically have fewer facial creases (wrinkles) than others of their age. Fibrosis can also occur in the cardiovascular system, respiratory system, and gastrointestinal tract, causing dysfunction in these systems.

Individuals with Myhre syndrome often have problems with the structure of the heart that are present at birth (congenital heart defects). Fibrosis in the cardiovascular system can lead to the development of additional problems such as high blood pressure (hypertension); narrowing (stenosis) of the heart valves or blood vessels; tightening of the pericardium, which is the membrane that surrounds the heart (constrictive pericarditis); or restrictive cardiomyopathy, in which the heart muscle is stiff and cannot fully relax after each contraction.

In Myhre syndrome, fibrosis of the respiratory tract can lead to narrowing of the windpipe (laryngotracheal stenosis) and the passages leading from the windpipe to the lungs (bronchi), high blood pressure in the vessels that carry blood from the heart to the lungs (the pulmonary arteries), damage to lung tissue (interstitial pulmonary disease), and an impairment of lung expansion (restrictive pulmonary disease). In the gastrointestinal tract, fibrosis can result in narrowing of the lower part of the stomach
(pyloric stenosis) or of the upper part of the small intestine (duodenal strictures), or severe constipation.

Growth is reduced in people with Myhre syndrome, beginning before birth and continuing through adolescence. Affected individuals have a low birth weight and are generally shorter than about 97 percent of their peers throughout life. They have shortened long bones of the arms and legs, and unusually short fingers and toes (brachydactyly). Other skeletal abnormalities associated with this disorder include thickening of the skull bones, flattened bones of the spine (platyspondyly), broad ribs, and underdevelopment of the wing-shaped structures of the pelvis (hypoplastic iliac wings). Affected individuals often have joint problems (arthropathy), including stiffness and limited mobility.

Typical facial features in people with Myhre syndrome include narrow openings of the eyelids (short palpebral fissures), deeply set eyes, a shortened distance between the nose and upper lip (a short philtrum), a narrow mouth with a thin upper lip, an underdeveloped upper jaw, and a protruding lower jaw (prognathism). Some affected individuals are born with an opening in the roof of the mouth (a cleft palate), a split in the lip (a cleft lip), or both. Vision problems are common in this disorder and can include eyes that do not point in the same direction (strabismus), nearsightedness (myopia), farsightedness (hyperopia), an irregular curvature of the front of the eye (astigmatism), clouding of the lenses (cataracts), or an abnormality of the back of the eye called pseudopapilledema.

Frequency

Myhre syndrome is a rare disorder; its prevalence is unknown. At least 60 cases have been documented in the medical literature.

Genetic Changes

Mutations in the SMAD4 gene cause Myhre syndrome. The SMAD4 gene provides instructions for making a protein involved in transmitting chemical signals from the cell surface to the nucleus. This signaling pathway, called the transforming growth factor beta (TGF-β) pathway, allows the environment outside the cell to affect gene activity and protein production within the cell. As part of this pathway, the SMAD4 protein interacts with other proteins to control the activity of particular genes. These genes influence the development of many body systems.

Studies suggest that the SMAD4 gene mutations that cause Myhre syndrome result in an abnormally stable SMAD4 protein that remains active in the cell longer than it is needed. Increased SMAD4 availability allows the protein more time to interact with other proteins and may result in abnormal TGF-β signaling in many cell types, which affects development of several body systems and leads to the signs and symptoms of Myhre syndrome.
Inheritance Pattern
This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

Other Names for This Condition
- LAPS syndrome
- laryngotracheal stenosis, arthropathy, prognathism, and short stature

Diagnosis & Management

Genetic Testing
- Genetic Testing Registry: Myhre syndrome

Other Diagnosis and Management Resources
- Centers for Disease Control and Prevention: Types of Hearing Loss
  https://www.cdc.gov/NCBDDD/hearingloss/types.html
- GeneReview: Myhre Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK425723

General Information from MedlinePlus
- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus
- Encyclopedia: Pericarditis -- constrictive
  https://medlineplus.gov/ency/article/001103.htm
- Encyclopedia: Short Stature
  https://medlineplus.gov/ency/article/003271.htm
• Health Topic: Developmental Disabilities
  https://medlineplus.gov/developmentaldisabilities.html

• Health Topic: Hearing Disorders and Deafness
  https://medlineplus.gov/hearingdisordersanddeafness.html

Genetic and Rare Diseases Information Center
• Myhre syndrome

Additional NIH Resources
• Eunice Kennedy Shriver National Institute of Child Health and Human Development: Intellectual and Developmental Disabilities
  https://www.nichd.nih.gov/health/topics/idds

Educational Resources
• Centers for Disease Control and Prevention: Intellectual Disability Fact Sheet

• Centers for Disease Control and Prevention: Types of Hearing Loss
  https://www.cdc.gov/NCBDDD/hearingloss/types.html

• Disease InfoSearch: Myhre syndrome
  http://www.diseaseinfosearch.org/Myhre+syndrome/9782

• MalaCards: myhre syndrome
  http://www.malacards.org/card/myhre_syndrome

• Orphanet: Myhre syndrome
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=2588

• Washington University in St. Louis Neuromuscular Disease Center
  https://neuromuscular.wustl.edu/mother/mlarge.html#myhre

Patient Support and Advocacy Resources
• American Heart Association
  http://www.heart.org/HEARTORG/

• Little People of America
  http://www.lpaonline.org/

• Little People UK
  http://littlepeopleuk.org/

• National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/myhre-syndrome/

• The Arc: for People with Intellectual and Developmental Disabilities
  https://www.thearc.org/
GeneReviews

- Myhre Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK425723

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28myhre+syndrome%5BTIAB%5D%29+OR+%28laps+syndrome%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D

OMIM

- MYHRE SYNDROME
  http://omim.org/entry/139210

MedGen

- Myhre syndrome

Sources for This Summary

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  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3257749/

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/27562837

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22158539

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24580733


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