Myhre syndrome

Description

Myhre syndrome is a rare condition that affects connective tissue. Connective tissue provides strength and flexibility to structures throughout the body. Myhre syndrome has a variety of signs and symptoms that affect many parts of the body, though not everyone has all the possible features. The features of the condition can range in severity, and some features become more apparent with age.

Common signs and symptoms of Myhre syndrome include short stature, skeletal abnormalities, limited joint mobility, characteristic facial features, intellectual and behavioral problems, hearing loss, a tendency for the buildup of scar tissue (fibrosis) in the skin and internal organs, and heart and lung abnormalities.

Growth is reduced in most people with Myhre syndrome, beginning before birth and continuing through adolescence. Affected individuals usually 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, unusually short fingers and toes (brachydactyly), and curved pinky fingers (fifth finger clinodactyly). 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 rarely, an abnormality of the back of the eye called pseudopapilledema.

Children with Myhre syndrome have delayed development, which is noticeable by age 5. Speech and language delay are the most significant. Motor skills such as crawling and walking may be delayed, although children with Myhre syndrome eventually learn to walk. Most affected individuals have intellectual disability that ranges from mild to

moderate, yet some are able to have jobs or pursue higher education.

People with Myhre syndrome typically have features like those in autism spectrum disorder, which affects communication and social interaction. These problems vary in severity, and they usually improve over time.

Hearing loss occurs in most people with Myhre syndrome, usually beginning in childhood and gradually worsening. If not detected promptly, hearing problems can contribute to learning and behavioral problems.

Fibrosis in Myhre syndrome can occur in the absence of injury (spontaneously) or develop following surgery or trauma. Affected individuals typically have stiff, thickened skin, usually beginning in childhood. Typically, 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. Scars may be more noticeable or become unusually thickened after healing (keloids or hypertrophic scars).

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

Abnormalities of the lungs and airways (respiratory tract) in people with Myhre syndrome include narrowing of the windpipe (laryngotracheal stenosis) and the passages leading from the windpipe to the lungs (bronchi); difficulty filling the lungs with air when inhaling (restrictive pulmonary disease); or widespread lung damage (interstitial lung disease). These respiratory tract problems can be life-threatening.

Additional features of Myhre syndrome include problems in the gastrointestinal tract, such as narrowing of the lower part of the stomach (pyloric stenosis) or of the upper part of the small intestine (duodenal strictures) and severe constipation. People with Myhre syndrome also may have an increased risk of developing cancerous or noncancerous tumors, including cancer of the lining of the uterus (endometrial cancer).

Frequency

Myhre syndrome is a rare disorder; its prevalence is unknown. Almost 100 cases have been documented in the medical literature.

Causes

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.

Learn more about the gene associated with Myhre syndrome

- SMAD4

Inheritance

Myhre syndrome is inherited in an autosomal dominant pattern, which means one copy of the altered *SMAD4* gene in each cell is sufficient to cause the disorder.

In almost all cases, the condition results from new mutations in the gene and occurs in people with no history of the disorder in their family. Rarely, an affected person inherits the mutation from one affected parent.

Other Names for This Condition

- LAPS syndrome
- Laryngotracheal stenosis, arthropathy, prognathism, and short stature

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Myhre syndrome (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0796081/)

Genetic and Rare Diseases Information Center

- Myhre syndrome (https://rarediseases.info.nih.gov/diseases/2572/index)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Clinical Trials

- ClinicalTrials.gov (https://clinicaltrials.gov/search?cond=%22Myhre syndrome%22)

Catalog of Genes and Diseases from OMIM

- MYHRE SYNDROME; MYHRS (https://omim.org/entry/139210)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28myhre+syndrome%5BTIAB%5D%29+OR+%28laps+syndrome%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+%22last+3600+days%22%5Bdp%5D)

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