Marrinesco-Sjogren Syndrome

Authored by

mohammad looti

October 1, 2025

Marrinesco-Sjogren Syndrome

Primary Disciplinary Field(s): Genetics, Pediatrics, Metabolic Diseases, Lysosomal Storage Disorders

1. Core Definition and Nomenclature

The term "Marrinesco-Sjogren syndrome," as presented in the provided source content, is identified as an alternative name for Mucopolysaccharidosis Type VI (MPS VI), more commonly known as Maroteaux-Lamy syndrome. It is crucial to note that historically and medically, Marinesco-Sjögren syndrome (with the standard spelling "Marinesco") refers to a distinct, rare autosomal recessive neurological disorder characterized by cerebellar ataxia, congenital cataracts, muscle weakness, and intellectual disability, which is entirely separate from MPS VI. The association of "Marrinesco-Sjogren syndrome" with MPS VI, as stated in the source, appears to be an unusual or potentially erroneous nomenclature for Maroteaux-Lamy syndrome.

Despite this potential terminological confusion, this entry will focus on the condition the source identifies with the term: Mucopolysaccharidosis Type VI (MPS VI), or Maroteaux-Lamy syndrome. MPS VI is a severe, progressive, inherited lysosomal storage disorder caused by a deficiency in the enzyme arylsulfatase B (ARSB), also known as N-acetylgalactosamine-4-sulfatase. This enzyme is vital for the breakdown of large sugar molecules called glycosaminoglycans (GAGs), specifically dermatan sulfate. When ARSB is deficient, dermatan sulfate accumulates within the lysosomes of various cells throughout the body, leading to cellular dysfunction, tissue damage, and a wide array of systemic clinical manifestations affecting multiple organ systems.

2. Etymology and Historical Context

The syndrome primarily referred to as Maroteaux-Lamy syndrome, or Mucopolysaccharidosis Type VI, derives its name from the French physicians Pierre Maroteaux and Maurice Lamy, who first described the condition in 1963. Their seminal work characterized a distinct form of mucopolysaccharidosis with specific enzymatic and clinical profiles, differentiating it from other known MPS types. This discovery was a significant step in the understanding and classification of lysosomal storage disorders, highlighting the diverse genetic and biochemical etiologies underlying these conditions. The official classification as Mucopolysaccharidosis Type VI (MPS VI) followed advancements in biochemical diagnostics, which identified the specific enzyme deficiency responsible for the disorder.

In contrast, the actual Marinesco-Sjögren syndrome is named after the Romanian neurologist Gheorghe Marinescu, who first described the condition in 1931, and the Swedish psychiatrist and geneticist Torsten Sjögren, who provided further clinical characterization in 1950. The historical development of these two distinct syndromes underscores the complexity of medical nomenclature

and the importance of precise diagnostic criteria to avoid confusion, particularly in the realm of rare genetic diseases where accurate identification is paramount for appropriate patient care and research.

3. Pathophysiology

The fundamental defect in Maroteaux-Lamy syndrome (MPS VI) lies in the gene encoding arylsulfatase B (ARSB), also known as N-acetylgalactosamine-4-sulfatase. This gene, located on chromosome 5q13-q14, when mutated, leads to a significant reduction or complete absence of functional ARSB enzyme activity. ARSB is a lysosomal hydrolase, meaning it functions within the lysosomes, the "recycling centers" of cells, to break down complex molecules into simpler components. Specifically, ARSB is responsible for the stepwise degradation of dermatan sulfate, a type of glycosaminoglycan (GAG) that is an essential component of connective tissues, skin, blood vessels, and cartilage.

Without adequate ARSB activity, dermatan sulfate cannot be properly catabolized and instead accumulates within the lysosomes of various cell types throughout the body, including fibroblasts, chondrocytes, hepatocytes, splenocytes, and vascular endothelial cells. This accumulation causes the lysosomes to swell, disrupting normal cellular function and metabolism. The engorged lysosomes interfere with cellular trafficking, signaling pathways, and ultimately lead to cell death or impaired cellular activity. The progressive accumulation of GAGs in tissues and organs results in widespread systemic damage, manifesting as the diverse and debilitating symptoms characteristic of MPS VI. The severity of the disease often correlates with the residual enzyme activity; lower activity typically leads to a more severe phenotype.

4. Clinical Manifestations and Progression

The clinical presentation of Maroteaux-Lamy syndrome (MPS VI) is highly variable, ranging from severe, rapidly progressive forms to attenuated, slowly progressive types. Symptoms typically become apparent in early childhood, although attenuated forms may not be diagnosed until later adolescence or adulthood. The source content highlights several key physical symptoms, which include macrocephaly, hydrocephalus, coarse facial features, heart valve disease, enlarged liver and spleen (hepatosplenomegaly), and umbilical hernia. Expanding on these, the manifestations span multiple organ systems:

Skeletal Abnormalities: Patients typically develop dysostosis multiplex, a characteristic pattern of skeletal deformities. This includes short stature, progressive joint stiffness (especially in large joints like hips and shoulders), leading to limited mobility, and spinal involvement such as kyphosis and scoliosis. Pectus carinatum (pigeon chest) or pectus excavatum (funnel chest) may also be present, affecting respiratory function.

Cardiac Involvement: Heart valve disease, particularly involving the mitral and aortic valves, is a common and serious complication, often leading to progressive valve thickening and dysfunction, which can result in heart failure. Other cardiac issues include cardiomyopathy and coronary artery disease due to GAG accumulation in the vessel walls.
Ocular Manifestations: Corneal clouding is almost universally observed in MPS VI and can significantly impair vision, often requiring corneal transplantation. Other ocular issues may include glaucoma and retinal degeneration.
Hepatosplenomegaly and Abdominal Issues: The accumulation of GAGs in the liver and spleen leads to their enlargement (hepatosplenomegaly), which can cause discomfort and abdominal distension. Umbilical and inguinal hernias are also common due to weakened connective tissues.
Neurological Involvement: While Maroteaux-Lamy syndrome typically does not involve primary intellectual disability (a key differentiator from many other MPS types), patients can develop neurological complications. These include hydrocephalus, caused by impaired cerebrospinal fluid (CSF) reabsorption due to GAG accumulation in the meninges, leading to increased intracranial pressure. Spinal cord compression, particularly in the cervical region, can occur due to skeletal deformities or GAG deposition, causing myelopathy and neurological deficits. Carpal tunnel syndrome is also common due to GAG infiltration compressing peripheral nerves.
Respiratory and Other Features: Coarse facial features, often described as "gargoylism," are characteristic, including a flattened nasal bridge, thick lips, and an enlarged tongue (macroglossia). Respiratory problems can arise from airway obstruction due to thickened tissues, recurrent respiratory infections, and restrictive lung disease from skeletal deformities. Hearing loss is also frequently observed.

5. Genetics and Inheritance

Maroteaux-Lamy syndrome (MPS VI) is an autosomal recessive disorder. This means that an individual must inherit two copies of the mutated ARSB gene, one from each parent, to develop the condition. Parents who carry one copy of the mutated gene are typically asymptomatic carriers and do not exhibit symptoms of the disease. If both parents are carriers, there is a 25% chance with each pregnancy that their child will inherit two copies of the mutated gene and develop MPS VI, a 50% chance that the child will be an asymptomatic carrier, and a 25% chance that the child will inherit two normal copies of the gene and be unaffected.

The ARSB gene is located on chromosome 5. Over 100 different mutations in the ARSB gene have been identified that can lead to MPS VI, highlighting the genetic heterogeneity of the disorder. The specific mutation(s) an individual carries can influence the residual enzyme activity and, consequently, the clinical phenotype, explaining the wide spectrum of disease severity observed. Genetic counseling is crucial for affected families to understand the inheritance pattern, assess recurrence risk, and explore reproductive options, including prenatal diagnosis or preimplantation genetic diagnosis (PGD).

6. Diagnosis

The diagnosis of Maroteaux-Lamy syndrome (MPS VI) typically involves a multi-step approach, beginning with clinical suspicion based on the characteristic physical findings. Initial screening often involves measuring glycosaminoglycan (GAG) levels in urine. Patients with MPS VI will typically show elevated levels of dermatan sulfate in their urine, which can be further confirmed by GAG electrophoresis or quantitative analysis. However, elevated urinary GAGs can be indicative of any MPS disorder, so specific enzyme testing is necessary for definitive diagnosis.

The gold standard for diagnosis involves enzyme assays, which measure the activity of arylsulfatase B (ARSB) in cultured fibroblasts, leukocytes, or dried blood spots. A significantly reduced or absent ARSB activity confirms the diagnosis of MPS VI. To rule out other MPS types that may present similarly, it is often prudent to test for multiple lysosomal enzymes. Finally, genetic testing involves sequencing the ARSB gene to identify specific mutations. Genetic confirmation is particularly useful for carrier identification, prenatal diagnosis, and in cases where enzyme activity results are ambiguous. Prenatal diagnosis can be performed via amniocentesis or chorionic villus sampling (CVS), allowing for early detection and family planning.

7. Treatment and Management

While there is currently no cure for Maroteaux-Lamy syndrome (MPS VI), significant advancements in treatment have transformed the prognosis for affected individuals. The primary specific therapy is Enzyme Replacement Therapy (ERT) with recombinant human arylsulfatase B (elosulfase alfa, marketed as Naglazyme). ERT involves intravenous infusions of the missing enzyme, which is taken up by cells and transported to the lysosomes, where it helps to break down accumulated dermatan sulfate. ERT has been shown to improve various aspects of the disease, including walking capacity, respiratory function, joint mobility, and reduction in liver and spleen size. It can also slow the progression of cardiac and skeletal manifestations, though its ability to cross the blood-brain barrier is limited, meaning it has less impact on central nervous system complications like hydrocephalus or spinal cord compression.

Beyond ERT, management is largely symptomatic and supportive, requiring a multidisciplinary approach involving specialists in cardiology, orthopedics, ophthalmology, pulmonology, neurology, and physical therapy. Surgical interventions may be necessary for complications such as heart valve replacement, carpal tunnel release, spinal decompression, or hydrocephalus management (e.g., ventriculoperitoneal shunting). Physical and occupational therapy are crucial to maintain joint mobility and improve functional independence. Regular monitoring of cardiac function, vision, hearing, and skeletal development is essential for timely intervention. Hematopoietic stem cell transplantation (HSCT) has also been explored, particularly in younger patients, and can provide a source of healthy cells that produce functional enzyme, but it carries significant risks and is

typically considered only for specific cases or as an alternative to ERT.

8. Prognosis and Long-Term Outlook

The natural history of untreated Maroteaux-Lamy syndrome (MPS VI) is one of progressive deterioration and significantly shortened lifespan, often due to cardiorespiratory complications. However, with the advent of Enzyme Replacement Therapy (ERT), the prognosis for individuals with MPS VI has substantially improved. Patients receiving ERT from an early age often experience a slower disease progression and a better quality of life compared to their untreated counterparts. ERT can mitigate many of the peripheral manifestations, such as hepatosplenomegaly, joint stiffness, and cardiac disease, thereby extending lifespan and enhancing functional abilities.

Despite these advancements, MPS VI remains a chronic, progressive condition. Central nervous system involvement, particularly spinal cord compression and hydrocephalus, often requires ongoing management and can significantly impact long-term neurological outcomes, as ERT does not effectively cross the blood-brain barrier. Individuals with more severe genotypes may still face significant challenges, even with treatment. Lifelong monitoring, consistent adherence to therapy, and a proactive multidisciplinary care approach are critical for optimizing outcomes. Continued research into gene therapy and novel therapeutic strategies holds promise for further improving the long-term outlook and potentially offering a cure for this complex genetic disorder.

9. Debates and Challenges in Management

Despite the therapeutic success of Enzyme Replacement Therapy (ERT) for Maroteaux-Lamy syndrome (MPS VI), several challenges and debates persist in its management. One significant challenge is the high cost of ERT, which can create barriers to access for patients in many healthcare systems globally, raising questions of equitable care. Furthermore, while ERT effectively addresses peripheral symptoms, its limited ability to cross the blood-brain barrier means that neurological manifestations, such as spinal cord compression and hydrocephalus, often require separate and invasive surgical interventions. This highlights the need for therapies that can target the central nervous system effectively.

Another debate revolves around the optimal timing of treatment initiation. Early diagnosis and intervention, ideally before irreversible organ damage occurs, are generally considered beneficial for maximizing therapeutic efficacy. However, the rarity of the disease and the variability in symptom onset can lead to diagnostic delays, especially in attenuated forms. Moreover, the long-term effectiveness and potential side effects of lifelong ERT, particularly concerning immune responses to the exogenous enzyme, require ongoing evaluation. The development of more effective therapies, including gene therapy approaches that could potentially offer a one-time cure

by correcting the underlying genetic defect, remains an active area of research and discussion within the medical and scientific communities.

10. Significance and Impact

Maroteaux-Lamy syndrome (MPS VI), alongside other lysosomal storage disorders, holds significant importance in both clinical medicine and biomedical research. For affected individuals and their families, the diagnosis profoundly impacts their lives, necessitating lifelong medical care, therapeutic adherence, and adaptation to chronic health challenges. The complexity and multisystemic nature of MPS VI underscore the need for a highly coordinated multidisciplinary care team, which can be a significant burden on families and healthcare resources. Patient advocacy groups play a crucial role in providing support, disseminating information, and advocating for research and access to treatments, thereby empowering affected communities.

From a scientific perspective, the study of MPS VI has contributed significantly to understanding fundamental cellular processes, particularly lysosomal function and glycosaminoglycan metabolism. The development of Enzyme Replacement Therapy (ERT) for MPS VI represents a landmark achievement in rare disease treatment, serving as a paradigm for developing therapies for other genetic disorders. Ongoing research into novel therapeutic strategies, such as gene therapy, substrate reduction therapy, and chaperone therapy, continues to advance the field, offering hope for improved outcomes and potentially even curative interventions. The insights gained from studying MPS VI not only benefit those directly affected by this rare condition but also deepen our understanding of more common diseases that involve similar cellular pathways or metabolic dysfunctions.

Further Reading

GeneReviews - Mucopolysaccharidosis Type VI
National Institute of Neurological Disorders and Stroke (NINDS) - Marinesco-Sjögren Syndrome
Genetic and Rare Diseases Information Center (GARD) - Mucopolysaccharidosis Type VI
Wikipedia - Maroteaux-Lamy syndrome
PMC (PubMed Central) - Elosulfase Alfa: A Review in Mucopolysaccharidosis VI (Maroteaux-Lamy Syndrome)