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Review Article

An Integrative Review of Mucopolysacchrodosis: Diagnosis, Genetic Foundation and Clinical Management

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ABSTRACT

Mutations in genes that code for lysosomal proteins results in a group of more than 70 inherited metabolic diseases called Lysosomal storage disorder. Lack of specific lysosomal enzymes affect breakdown of glycosaminoglycans (GAGs) long heteropolysaccharides made up of repeating disaccharide monomers present in connective and other tissues resulting in Mucopolysaccharidoses (MPS) that is a rare type of LSD . Accumulation of GAG in various body parts is responsible for the clinical symptoms of MPS. Flattened face, a sunken nasal bridge, thick lips, and an enlarged mouth are examples of dysmorphic facial features observed frequently in MPS patients . Eleven enzyme deficiencies that cause seven distinct clinical types of MPS have been identified (MPS I (subtypes: Hurler, Hurler-Scheie, Scheie); MPS II; MPS III (subtypes: IIIA, IIIB, IIIC, IIID); MPS IV (subtypes IVA, IVB); MPS VI; MPS VII; MPS IX). All these MPS disorders are inherited in an autosomal recessive manner apart from MPS II, which is X-linked. Hurler syndrome, also referred as mucopolysaccharidosis type I (MPS I), is one of the eleven mucopolysaccharidoses (MPS) disorders occurs due to lack of alpha-L-iduronidase , lack of the enzyme results in the accumulation of dermatan sulfate and heparin sulfate in multiple tissues. Hunter syndrome (also known as mucopolysaccharidosis Type II [MPS II]) is a lysosomal storage condition caused by a lack of iduronate-2-sulfatase.Morquio syndrome (mucopolysaccharidosis type IV; MPS IV) is a mucopolysaccharide storage disease has two variants (Morquio syndromes A and B) which is caused due to lack of the enzymes N-acetyl-galactosamine- 6-sulfatase and beta-galactosidase. Mucopolysaccharidosis type VII (Sly syndrome) occurs due to lack of enzyme β-glucuronidase. MPS IX (Narowictz Syndrome) is an extremely rare type of MPS occurs due to lack of in the lysosomal enzyme hyaluronidase, causing build up of hyaluronan.

INTRODUCTION

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Lysosomal Storage Disease

Lysosome is a sub-cellular organelle that is found in nearly all types of eukaryotic cells and that is responsible for the digestion of macromolecules, old cell parts, and microorganisms.[1] Mutations in gees that code for lysosomal proteins results in a group of more than 70 inherited metabolic diseases called Lysosomal storage disorder. The majority of these proteins are lysosomal hydrolases, accessory proteins, membrane transporters, or trafficking proteins.[3] The metabolic pathway within the lysosome for breakdown of different classes of macromolecules has a compulsory order of enzymatic steps. Therefore, the absence of one enzyme's activity, due to deleterious mutation in its gene, will result blockage of the pathway and the reuniting progressive accumulation or storage of partially digested material within the lysosome is the basis for lysosomal storage disease [2].

Defective enzyme are a result of various kinds of mutations. A nonsense mutation usually presents increased significant defect than a missense mutation.[4] LSDs are classified based on the type of storage material into sub-categories namely: sphingolipidoses, mucopolysaccharidoses, glycoproteinases, lipid storage disease, and glycogen storage disease. Also, based on the age of onset of initial symptoms, they are classed into infantile, juvenile, and adult-onset forms.[3]

Mucopolysaccharidosis-

Lack of specific lysosomal enzymes affect breakdown of glycosaminoglycans (GAGs) that long heteropolysaccharides made up of repeating disaccharide monomers present in connective and other tissues resulting in Mucopolysaccharidoses (MPS) that is a rare type of LSD . These GAGs include dermatan sulfate, heparan sulfate, keratan sulfate, chondroitin sulfate, and hyaluronic acid are examples of GAGs. A wide range of clinical manifestations occur due to the build up GAGs in patients's organs and tissues involving the eye, central nervous system, skeletal, ocular, nervous, respiratory, cardiac, and the gastrointestinal system causes a wide range of clinical manifestations. [5] [6]. Accumulation of GAG in various body parts is responsible for the clinical symptoms of MPS. Flattened face, a sunken nasal bridge, thick lips, and an enlarged mouth are examples of dysmorphic facial features observed frequently in MPS patients . In addition, patients may simultaneously also have conditions like serious neurological and intellectual issues, hearing impairment, bone disease, cardiorespiratory disease, and severe neurological and intellectual abnormalities.[7]

Classification Of Mucopolysaccrodosis

Eleven enzyme deficiencies that cause seven distinct clinical types of MPS have been identified (MPS I (subtypes: Hurler, Hurler-Scheie, Scheie); MPS II; MPS III (subtypes: IIIA, IIIB, IIIC, IIID); MPS IV (subtypes IVA, IVB); MPS VI; MPS VII; MPS IX). All these MPS disorders are inherited in an autosomal recessive manner apart from MPS II, which is X-linked [5]

Table 1.1 : classification of mucopolysaccharidosis

Types	Sub Type	Deficient Enzyme	Accumulated Gag
Mps-I (Hurler Syndrome)	Hurler Syndrome	α-L-Iduronidase	Heparan Sulphate Dermatan Sulphate
	Hurler-Scheie Syndrome	α-L-Iduronidase	Heparan Sulphate Dermatan Sulphate
	Scheie Syndrome	α-L-Iduronidase	Heparan Sulphate Dermatan Sulphate
Mps-Ii (Hunter Syndrome)		Iduronate-2-Sulfatase	Heparan Sulphate Dermatan Sulphate

Mps-Iii (Sanfillippo Syndrome)	A	Heparan-N-Sulfatase	Heparan Sulphate
	B	A-N-Acetylglucosaminidase	Heparan Sulphate
	C	Ɑ-Glucosaminidase Acetyl Transferase	Heparan Sulphate
	D	N-Acetylglucosamine 6-Sulfatase	Heparan Sulphate
Mps-Iv (Morquio Syndrome)	A	N-Acetylgalactosesamine 6-Sulfatase	Chondrotrin-6-Sulfate Keratan Sulfate
	B	B-Galactosidase	Keratan Sulfate
Mps-Vi (Maroteaux-Lamy Syndrome)		N-Acetylgalactosamine-4-Sulfatse	Chondrorin-4-Sulfate Dermatan Sulphate
Mps-Vii (Sly. Sundrome)		B-D-Glucuronidase	Heparan Sulphate Dermatan Sulphate Chondrotin-6-Sulfate Chondrotin-4-Sulfate
Mps-Ix (Natowicz Syndrome)		Hyaluronidase	Hyaluronan

Hurlers Syndrome

Hurler syndrome, also referred as mucopolysaccharidosis type I (MPS I), is one of the eleven mucopolysaccharidoses (MPS) disorders. It was previously known as gargoylism. It is an inherited lysosomal disorder which occurs due to lack of alpha-L-iduronidase (an enzyme responsible for the breakdown of glycosaminoglycans GAGs or mucopolysaccharides). Lack of the enzyme results in the accumulation of dermatan sulfate and heparin sulfate in multiple tissues, leading to progressive deterioration and eventually, death.

Genetic basis

Mutations in the α-L-iduronidase (IDUA) gene results in an autosomal recessive disease called Mucopolysaccharidosis type I (MPS-I). Glycosidase α-L-iduronidase (IDUA) enzyme deficiency occurs due to these mutations, this enzyme is required for the degradation of heparan sulphate and dermatan sulphate, deficiency of enzyme results in subsequent storage of these glycosaminoglycans in the lysosome [(8)]. There is a broad range of clinical phenotypes in MPS-I (eponyms: Hurler syndrome, severe; Hurler/Scheie syndrome, intermediate; Scheie syndrome, mild), making prediction of disease severity and genetic counselling challenging furthermore it is also difficult to differentiate between these subtypes via biochemical measurement [(8),(9)]

Clinical Presentation-

A significant amount of diversity might be present in MPS-I presentation and course. This might be

because patients vary in the severity of the underlying mutation(s) and the resulting residual enzymatic activity, however, there may also be other factors contributing to the well-known phenotypic heterogeneity.[2] Historically, MPS I is a subdivided into three syndromes—Hurler, Hurler–Scheie, and Scheie—although it is now widely recognized that these subtypes possess similarity when it comes to symptomatology.

- Hurler syndrome is the most severe type of MPS I, it is characterized by coarse facial features, joint stiffness and contractures, short stature, additionally delay in development, cognitive impairment, respiratory, cardiac and hepatic aliments may occur.
- Scheie syndrome has delayed onset of symptoms that are milder and a slow course of disease progression. Even though patients with the Scheie phenotype may show substantial disease-related morbidity, they often exhibit normal intelligence and make it to adulthood.
- Hurler–Scheie syndrome is an intermediate phenotype which has little or no cognitive impairment and somatic symptoms that lower life expectancy into the second or third decade of life. (10)

Orofacial features- Delayed tooth emergence, malocclusion, taurodontism, hypodontia, microdontia, Gingival hyperplasia, radiolucency in maxilla / mandible, condylar abnormalities.(11)

Sensory functioning- impairment of hearing, otological ailment, clouding of the cornea.(12)

Cognition- The majority of the children assessed during their initial years preserved cognitive function. Nonetheless, when compared to normally growing children these patients demonstrate reduced cognitive ability. Cognitive development in children with Hurler syndrome children's cognitive development began to vary from usual development at approximately 9 months of age (12)

Respiratory- Respiratory problems often are seen shortly after birth, may need respiratory support during the new born stage. noisy breathing or snoring, apneic episodes.(12)

Cardiovascular- cardiac valve disease: early-onset severe regurgitation and stenosis, coronary artery disease, cardiomegaly: initially hypertrophic then dilated. (13)

Neurological abnormalities- macrocephaly prominent perivascular spaces, cerebral atrophy, diffuse white matter changes, hydrocephalus, pachymeningiopathy and J-shaped Sella.(13)

Diagnosis-

MPS is difficult to diagnose because of the disease's rarity as well as the variability of clinical manifestations, many of the early disease features represent common childhood symptoms (eg, inguinal/umbilical hernia and recurrent upper respiratory tract infections), making diagnosis solely based on early symptom is challenging. Newborn screening (NBS) method ought to be more successful in this respect. NBS programs for MPS start with evaluation of IDUA activity measured directly from the dried blood spot. Fluorometric, digital microfluidics, and tandem mass spectrometry-based analyses are the screening assays that are used. Screening for MPS I can be incorporated in multiple assay screening done for multiple lysosomal storage disorders in a single DBS sample. All DBS-positive newborn samples should further undergo IDUA enzyme analysis (from fresh blood leukocytes, serum, or plasma). In case of a positive confirmatory enzyme assay, patients must be immediately evaluated by a genetic/metabolic disease specialist for additional clinical, molecular, and biochemical testing. After the conformation of reduced or inadequate *IDUA* enzyme activity, gene sequencing, biochemical assessment, and a comprehensive clinical examination should be conducted. Most laboratories nowadays employ

dye-binding methodology to assess uGAG quantitively [14]

Treatment And Management-

Mucopolysaccharidoses (MPSs) are multiorgan debilitating disorder for which the progression of the disease is being altered significantly by hematopoietic cell transplantation (HCT) and few times by enzyme replacement therapy.[15]

Enzyme replacement therapy*:* Weekly intravenous injection of Recombinant human alpha L- iduronidase (Aldurazyme) are administered. Early initiation of ERT has shown to postpone or lower disease severity in attenuated variants of MPS and increase survival in case of Hurler syndrome, decrease of GAG build up and alleviation of certain somatic symptoms is seen by use of Enzyme-replacement therapy (ERT) with laronidase . Nevertheless, the effectiveness ot ERT is limited as skeletal and CNS symptoms are not controlled, and anti-IDUA antibodies develop in most patients.[16] [17]

Hematopoietic stem cell transplant (HSCT): In HSCT donor-derived enzyme competent cells are used to replace enzyme-deficient hematopoietic cells. (HCT) treats the severe, neurodegenerative form (Hurler syndrome). It has been demonstrated that HCT can arrest neurologic deterioration, maintain cognitive function, enhance metabolic correction, and increase survival. [16] [17] Guidelines advice use of HCT MPS I, often ERT is used as an additional therapy to enhance the health status of patients ahead of HCT, and the primary goal of employing ERT in the peri transplant period is to lower morbidity and mortality associated with HCT. Also, these combined therapies have been linked with less severe cognitive decline after HCT [17]

New Therapies- There are other strategies suggested to deliver enzyme "hard-to-reach" tissues such as avascular connective tissue or tissues isolated from the circulation by a specific barrier (e.g., blood-brain barrier, blood-retina barrier) have been proposed. These comprise, (in order of their proximity to clinical use) gene therapy (GT), direct local administration, small molecule therapies, targeted enzyme-delivery systems, mesenchymal stem cell therapy, and focused ultrasound therapy.

Hunter Syndrome

For heparan sulfate and dermatan sulfate to be broken down by lysosomes, iduronate 2-sulfatase (IDS, EC3.1.6.13) is necessary. Human IDS deficiency mutations cause these glycosaminoglycans to be stored in the lysosomes. This storage leads to the clinical disorder known as Hunter Syndrome (also known as mucopolysaccharidosis type II, or MPS-II), in which patients can present with a range of phenotypes, from severe mental retardation, skeletal deformities, and stiff joints, to a relatively mild course. [18]

Genetic Basis-

Hunter syndrome (also known as mucopolysaccharidosis Type II [MPS II]) is a lysosomal storage condition caused by a lack of iduronate-2-sulfatase (IDS) that affects the X chromosome. [19]. Based on the age of onset and severity level, three clinical forms—mild, middle, and severe—are identified. It is assumed that the syndrome's clinical heterogeneity is caused by different mutations at the IDS locus that have an impact on the expression, stability, or function of the enzyme. The human IDS gene has nine exons and is located on chromosome Xq28.1. It is roughly 24 kb long. Following the sequencing of the entire IDS gene, an IDS-like pseudogene containing copies of exons 2 and 3 as well as intron 7 was discovered approximately 20 kilo-bases away from the active gene. The 1650 bp full-length cDNA codes for a 550 amino acid polypeptide that exhibits strong similarity with the sulfatase protein family. [20]

Clinical Presentation-

Massive cranium (dolichocephalic), short stature, mental retardation, coarse facial appearances, protuberant abdomens, broad noses with flaring nostrils, huge jaws, hypotonia, and large tongues are among the usual clinical manifestations, which appear between the ages of two and four. Additional clinical characteristics include infection of the upper respiratory tract, valvular heart disease resulting in hypertrophy of the left and right ventricles and heart failure, chronic diarrhoea, enlarged liver and spleen, umbilical and inguinal hernias, corneal clouding with impaired vision, and hearing loss due to both sensorineural and connective deficits. A communicative hydrocephalus is a frequent observation that may result in serious neurological symptoms. [(23)]The clinical presentation and rate of progression of the disease are highly variable. Somatic disease manifestations are present in all patients with MPS II; however, central nervous system (CNS) involvement manifests in about two-thirds of patients.[(21)] Multiple organs and tissues are impacted by Hunter syndrome, it is a chronic progressive condition with clinical presentation that vary significantly in severity. patients having the neuronopathic form of the disease also endure somatic symptoms, and may also exhibit developmental delay and cognitive impairment in early childhood which progressively worsens and can become severely life-limiting. Patients may suffer from secondary neurological symptoms such as hydrocephalus, vision and hearing loss, carpal tunnel syndrome and spinal cord compression. Despite the clinical manifestations of Hunter syndrome range from mild to severe form, patients are typically in one of two groups: those having the serious (neuronopathic) form of the disease and those having the milder (non-neuronopathic) form. Neuronopathic hunter syndromehas effected about two-thirds of patients Patients with neuronopathic Hunter syndrome have developmental delay and cognitive impairment, that begins in early childhood and progressively worsens, resulting in to early death in the second decade of life. Neurological signs and symptoms that may be evident in patients having either the neuronopathic or non-neuronopathic phenotypes include seizures, optic nerve compression, hearing impairment, sleep apnea, hydrocephalus, carpal tunnel syndrome, spinal cord compression and cervical myelopathy. Children with Hunter syndrome display a plateau in regard with their cognitive, language and motor which is followed by decline from the age of 4 years. Behavioural problems often precede cognitive decline and are often the first symptoms parents report. Behavioural problems include tantrums, obstinacy and hyperactivity and can be misdiagnosed as attention deficit hyperactivity disorder or other neurodevelopment disorders. Children having both forms of Hunter syndrome tend to have hearing loss and reduced mobility are seen in children with both forms of Hunter syndrome; these condition, along with declining cognitive function associated with neuronopathic disease, can aggravate behavioural issues and make patients frustrated .Hyperactivity decrease with age, but this due to patients decreased physical ability as the disease progresses. Patients may ultimately enter a vegetative state. Delays in speech development may occur in conjunction with cognitive decline in severely affected in children who are severely affected cognitive decline can alongside with delays in speech development, and many patients never acquire the ability to communicate using complete phrases.

Due to hearing loss, patients with non-neuronopathic disease may display a delay in language acquisition even though they have normal cognitive development.. In some patients, mild residual cognitive disability may occur secondary to early sensorial isolation.Thus identifying neuronopathic disease can be complicated in some individuals. Sleep

disturbances caused by either obstructive apnea or central apnea or both are three times more common in patients who have neuronopathic disease than in non-neuronopathic patients[22].

Diagnosis-

Clinical Diagnosis-The clinical diagnosis of Hunter syndrome firstly needs a comprehensive patient medical and family history. Paediatricians are likely to be the first clinicians to encounter a patient with Hunter syndrome, and there are multiple of early signs and symptoms of Hunter syndrome such as lumbar gibbus, recurrent ear infections, hernia, myocarditis, or progressive hepatosplenomegaly that should raise clinical suspicion in paediatricians , who are likely to be the first clinicians to encounter a patient with Hunter syndrome. These symptoms may develop a before the age of six months. [24]

Biochemical Diagnosis-

Urinary GAG analysis: Elevated levels of total urinary GAG (uGAG) is seen in MPS. Excess GAGs in the urine indicate the likely presence of an MPS, but is not a definitive diagnostic test for Hunter syndrome, and other tests should be performed.[24]

Enzyme assay: If uGAG analysis reveals increased dermatan and heparan sulfates levels, then definitive biochemical diagnosis is done by blood enzyme testing. Enzyme assays should be performed to determine deficiency of I2S enzyme activity in plasma leukocytes or fibroblast. [24]

Treatment And Management-

There are currently two major therapies for patients with MPS II; enzyme replacement therapy (ERT) and hematopoietic stem cell therapy (HSCT).[25]

Enzyme Replacement Therapy- A recombinant form of human I2S is used to treat MPS II .According to the clinical trials have shown that ERT improves visceral organ function measures of pulmonary function, walking ability, and lowers the urinary GAG levels. Conventional ERT has demonstrated to have some drawbacks :

1. Reduced efficacy for hard connective tissues due avascularity including bone and heart valves
2. Compliance is a hardship due to required weekly four- five hour intravenous infusions.[25]

Hematopoietic Stem Cell Therapy- HSCT has been demonstrated to be effective in the treatment of several MPS diseases and other LSDs. In Japan HSCT has been suggested as a part of routine treatment for MPS II , on visceral organs HSCT and ERT have similar efficacy to that of ERT If HSCT is given at an early stage before signs of brain atrophy and heart valve problems are seen, then HSCT has been exhibited effective in treating both brain (CNS involvement) and heart defects[25]

Gene Therapy- The new treatment for MPS II is gene therapy. It will be a one-time procedure with higher safety and efficacy profile because of which it will be better than both ERT and HSCT. A two-year trial, which has now been approved by the UK Medicines and Healthcare Products Regulatory Agency (MHRA), will be carried out at the Royal Manchester Children's Hospital.[26] [27]

Sanfilippo Syndrome

Sanfilippo syndrome, also known as mucopolysaccharidosis III, is a lysosomal storage illness brought on by mutations in the genes that break down the extracellular membrane glycosaminoglycan heparan sulfate. The primary phenotypic trait is severe central nervous system degeneration brought on by the accumulation of undegraded heparan sulfate molecules within lysosomes, which causes cellular malfunction and pathology in multiple organs.[28]

Genetic Basis

Because this disorder is inherited in an autosomal recessive manner, each cell's two copies of the gene have variations. One copy of the mutated

gene is carried by each parent of a person with an autosomal recessive disorder, but they usually do not exhibit the symptoms of the condition. MPS III is caused by variations (sometimes referred to as mutations) in the genes for SGSH, HGSNAT, NAGLU, and GNS. The production of enzymes involved in the degradation of big sugar molecules known as glycosaminoglycans (GAGs) is directed by these genes. The condition's name comes from the original term for GAGs, mucopolysaccharides. A subset of GAGs known as heparan sulfate is broken down step-by-step by the GNS, HGSNAT, NAGLU, and SGSH enzymes.[29]

- MPS IIIA is caused by variants in the SGSH gene,
- MPS IIIB is caused by NAGLU gene variants.
- MPS IIIC is caused by HGSNAT gene variants.
- GNS gene mutations cause MPS IIID.

Enzyme function is diminished or eliminated by variations in these genes. The breakdown of heparan sulfate is disrupted when any one of these enzymes is absent. Heparan sulfate that has been partially broken down consequently builds up inside cells, particularly inside the lysosomes. The cell's lysosomes are compartments that break down and recycle many kinds of chemicals. Lysosomal storage disorders include conditions like MPS III that result in the accumulation of chemicals within the lysosomes. Scientists think that the buildup of GAGs disrupts the regular processes of cells and interferes with the actions of other proteins within the lysosomes. Why the heparan sulfate accumulation mostly impacts the central nervous system in MPS III is unknown. [29]

(table 1.2: genes and enzymes responsible for occurrence of Sanfilippo syndrome type A to D)

Sanfilippo Syndrome Type	Gene	Enzyme
Type A	Sgsh	Heparan N-Sulfatase
Type B	Naglu	Alpha-N-Ace tylglucosaminidase
Type C	Hgsnat	Acetyl-Coa-Alpha-Glucosaminide-N-Acetyletranferase
Type D	Gns	N-Acetylglucosamnie-6-Sulfatase

Clinical Presentation

Extreme clinical variability is a hallmark of mucopolysaccharidosis type III (MPS III), a multisystem lysosomal storage disorder caused by glycosaminoglycan (GAG) buildup. The most noticeable symptom is progressive degradation of the central nervous system, which leads to significant intellectual impairment and developmental regression. The somatic manifestations typical of other mucopolysaccharidoses (MPSs) are frequently seen, but they are typically less noticeable in patients with MPS III.[30]

Children with Sanfilippo syndrome are born without clinical features of a metabolic disorder. In the toddler years, aggressive behaviours emerge, with marked hyperactivity and destructive tendencies. There may be somatic characteristics such minor organomegaly, little corneal clouding, and orthopedic problems. Children six years of age or older (and occasionally younger) are typically the first to exhibit neurologic deterioration. Death might not happen until puberty. [31] A poor prognosis and deteriorating clinical progression are hallmarks of Sanfilippo syndrome. Patients eventually experience CNS deterioration and enter

a vegetative state. The most common cause of death before the age of 20 is cardiac arrest brought on by airway blockage and/or pulmonary infection. The most severe variety is type IIIA, and the majority of its sufferers pass away in their teens. (31)

Craniofacial and physical appearance. Many children have dolichocephaly or macrocephaly. Thick alae nasi, lips, ear lobules or helices, and macroglossia are examples of dysmorphisms. It is common to see hirsutism, synophrys, and coarse, thick hair. Venipuncture can occasionally be challenging due to thick, tight skin. (30)

Neurologic: Ventriculomegaly hypothetically occurs secondary to cerebral atrophy and impaired reabsorption of cerebrospinal fluid. Some individuals may experience symptomatic hydrocephalus. Seizure disorders, are common during later disease stages, but are not universal. Progressive neurodegeneration can result in gait disorders, hyperactive reflexes, or spasticity. (30)

Development and cognition: Even while early childhood development may be typical, it is not unusual for language or other developmental deficits to appear as early as one year of age. Following a plateau in growth, a gradual decline in motor and cognitive abilities starts. Regression in fast advancing MPS III can begin as early as age three or four. Regression might not be noticeable in patients with extremely mild illness until much later. By the ages of 10 to 15, verbal skills are frequently lost, if language was learned. For those with a more severe course of the disease, loss of independent ambulation may begin earlier, but it usually happens between adolescence and the third decade. In the end, neurodegeneration results in unresponsiveness, immobility, and dysphagia.

Psychiatric and behavioral: MPS III's behavioral phenotype, which is frequently a defining feature of the illness, typically starts between the ages of three and five. Nearly all impacted kids are hyperactive and frequently don't respond to medicine. Outbursts and tantrums are examples of aggressive and destructive behaviors that are widespread and can be challenging to regulate, especially in people with typical strength and movement. As people age, their behavior becomes less bothersome because they lose initiative and mobility due to increasing neurodegeneration.(30) People with MPS III have been reported to exhibit Klüver-Bucy syndrome, a unique collection of neurobehavioral symptoms that includes psychic blindness, hypersexuality, disinhibition, hyperorality, and hyper transformation. Some people, especially those with later-onset or more slowly developing disease, are known to have early-onset dementia.

Sleep disturbances, present in 80%-95% of individuals, include difficulties with settling and frequent waking. These sleep disorders are thought to result from irregular sleep/wake patterns; some affected individuals demonstrate complete circadian rhythm reversal.

Musculoskeletal: Joint stiffness or contractures and features of dysostosis multiplex are common, although much less severe than in other MPS disorders. Skeletal manifestations are usually not clinically obvious until after the onset of developmental regression and behavioural concerns. Typically, skeletal abnormalities such as hip dysplasia and scoliosis are not severe enough to necessitate surgery. Hip discomfort is frequently caused by osteonecrosis of the femoral head. Trigger fingers and carpal tunnel syndrome are possible.

It is common to have low bone mass and vitamin D deficiency, which can be shown as early as adolescence. Individuals who have a history of anti-seizure medication use or reduced mobility are particularly vulnerable to osteoporosis and fractures.

Hearing loss: it is common and can be conductive, sensorineural, or mixed due to a combination of

dysostosis of the ossicles of the middle ear, inner ear abnormalities, and frequent otitis media.

ENT (otolaryngologic): Chronic and recurrent otitis media and rhinitis accompanied by poor sinus drainage are common as are frequent infections of the adenoids and tonsils, which may be enlarged.

Respiratory: Respiratory tract and sinopulmonary infections are common. Abnormal respiration can also be secondary to neurodegeneration, thick secretions with inefficient drainage, and anatomic airway obstruction. Rarely, the adenoids or tonsils are so enlarged that they cause obstructive sleep apnea. However, sleep apnea may also be due to the significant CNS involvement.

Gastrointestinal: Although the main cause is unknown, constipation and/or persistent or recurring loose stools are prevalent. Although it usually occurs in episodes, some people may experience continuous diarrhea. Activity and food may have an impact on these issues, and repeated antibiotic therapy for recurring infections may make them worse. Umbilical and inguinal hernias are frequent. Following surgery, inguinal hernias may recur. Unless they are large or create other health issues, umbilical hernias are typically not addressed. Many affected people experience dysphagia and/or difficulties chewing and swallowing food as their neurodegeneration worsens, which raises their risk of aspiration pneumonia and, in later stages of the disease, weight loss due to inadequate eating. [30]

Cardiovascular. The majority of people with MPS III do not need cardiac intervention, despite the fact that GAG storage in the myocardium, aortic valve, mitral valve, and/or cardiac conduction system (resulting in atrioventricular block) is prevalent. Children have a normal left ventricular ejection fraction, whereas adults have a little impairment. The low prevalence of clinical heart disease in this cohort to date may be explained by elderly people's shorter lifespans and decreased levels of exercise. [30]

Ophthalmologic: People with MPS III typically do not have corneal opacities, such as corneal clouding. However, especially in the latter stages of the disease, people with MPS III may experience retinal degeneration and optic nerve atrophy, which can present as pigmentary retinopathy, poor peripheral vision, and night blindness. [30]

Diagnosis

To diagnose MPS III, mucopolysaccharides are usually first measured in urine, followed by measurement of enzyme activity in blood or a small skin sample. Increased heparan sulfate in urine, and a decrease in the activity of any one of the four enzymes (shown in the table above) is usually consistent with a diagnosis of MPS III and will identify the MPS III type (A, B, C or D). It is important to know the MPS III type as many of the treatments being developed are only for specific types. Genetic testing of a blood sample will allow the identification of the exact changes in the DNA. It is important to attend genetic counselling to learn the implications for other children in the family, future pregnancies, and extended family members. The counsellor will explain the inheritance pattern and help advise who should be tested. If the genetic diagnosis is known, this information can be used to test other at-risk members of the family. It can also be used for prenatal testing of future pregnancies (testing a foetus while still in the womb) and/or preimplantation diagnosis (testing of embryos created through IVF to select those that do not carry the relevant gene mutation). [31] Two motivations for the creation of new screening techniques are decreasing the age at which it can be applied, and increasing output and/or decreasing cost, either by a simpler and more rapid method to detect a particular disease, or by an

increased scope in the number of diseases that can be diagnosed using the same test.[32]

Treatment And Management

Early diagnosis of Sanfilippo syndrome is critical to ensure the optimal care for patients and their families by enabling access to specific supportive interventions to maximize peak abilities, slow rate of decline, and improve quality of life. [33] Optimizing the quality of life for patients and their families should be the main objective of management in the absence of a disease-modifying treatment for Sanfilippo syndrome. This necessitates a comprehensive strategy that takes into account the many and intricate medical requirements of patients suffering from this illness. The formation of a multidisciplinary team of medical specialists to collaborate and partner with patients who have Sanfilippo syndrome and their families is a crucial step in this process. This multidisciplinary team might consist of doctors, nurses, therapists (such as occupational, speech, and physical therapists), dieticians, psychologists, social workers, special educators, and counselors, among others. Care coordination should be supervised by a supervising clinician. Every patient with Sanfilippo syndrome and their family should receive comprehensive care as soon as possible, preferably right after diagnosis. The frequency of clinic visits and evaluations should also be customized to each patient's specific needs. Frequent communication with families is important to align on care goals and plans, and to ensure that the best interests and values of patients and their families remain at the heart of the decision-making process. [33] In the light of the absence of available therapy for Sanfilippo syndrome, the only way to manage this disease is to keep patients in as good condition as possible for a relatively long time (taking into consideration the expected life span). There are two possible methods to achieve this,

i. optimized symptomatic treatment
ii. psychological care. [34]

Optimized Symptomatic Treatment

i. Risperidone treatment was suggested as a possible management of hyperactivity with some efficacy. [34]
ii. Sleep disorders are frequent in this disease, and the use of melatonin might allow patients to improve sleep deficits. It is important to test if sleep apnoea occurs, to support breathing mechanically if necessary. [34]
iii. Although Sanfilippo disease frequently causes bone, joint, and muscular abnormalities, these conditions are typically not as severe as those found in other kinds of MPS. However, patients' quality of life may be enhanced by symptomatic therapy of these illnesses. One possible pharmaceutical therapy is vitamin D supplementation. Surgery might be helpful, however, such intervention should always be considered carefully, as MPS III patients reveal an increased risk during anaesthesia. Moreover, the procedures should not be highly invasive due to very restricted contact with patients and their difficult convalescence after surgery. [34]
iv. Patients with MPS III frequently experience otorhinolaryngological symptoms, with acute otitis media, upper airway obstruction, hearing loss, and chronic or recurring rhinosinusitis being the most common consequences. Patients with MPS III have been documented to undergo procedures like tracheostomy, tympanostomy, and adenoidectomy.[34]
v. Gastrointestinal manifestations are common in MPS III patients, the most severe gastrointestinal complications in MPS III, reported to date, include bleeding from the digestive tract, haemorrhagic pancreatitis, perforation of the tract due to gastrostomies, paralytic ileus, and emaciation, however, it is

important to note that in many cases they can be effectively treated with antimicrobial agents and/or the use of probiotics, as reported for another MPS. [34]

Psychological Treatment

In psychological approach, it is crucial to focus on neurocognitive development of patients. In the light of the severity and progressive character of neurocognitive manifestations, early access to clinical and psychological services is crucial for the families with children suffering from Sanfilippo disease. These agencies ought to be ready to assist with this difficult, uncommon illness. The improvement of the family's overall quality of life depends on the neurocognitive evaluation of patients with Sanfilippo disease as well as on testing and family interviews. Support groups, psychoeducation, psychological treatment (including routine individual or group therapy), and the dissemination of trustworthy information by medical professionals are all required. In order to lessen the effects of sleep disturbance and, consequently, the wellbeing of the entire family, parents of children with Sanfilippo disease may also benefit from early sleep hygiene instruction.[34]

Morquio Syndrome-

Morquio syndrome (mucopolysaccharidosis type IV; MPS IV) is a mucopolysaccharide storage disease has two variants (Morquio syndromes A and B) which is caused due to lack of the enzymes N-acetyl-galactosamine- 6-sulfatase and beta-galactosidase. Types A and B Type A and Type B are the two forms of Morquio syndrome, which are both autosomal recessive disorders. The 16q24.3 gene encodes the disease Morquio syndrome 4A, which is caused by a deficiency of the galactosamine-6-sulfatase (GALNS) enzyme. The absence of beta galactosidase results in type 4B. Both forms of illness exhibit keratan sulphate and chondroitin 6 sulphate accumulation. [35]

Between the two variants, A and B, corresponding to deficiencies of two distinct enzymes. there is significant clinical variability due to the existence of attenuated phenotypes, of the two type A is typically severe.[35]

Genetic Basics-

Morquio A Syndrome - *N*-acetylgalactosamine-6-sulfatase (GALNS), is a lysosomal enzyme responsible for the hydrolytic breakdown of keratan sulfate and chondroitin-6-sulfate, insufficiency of this enzyme causes Mucopolysaccharidosis IV-A or Morquio A disease (MIM #253000] an autosomal recessive lysosomal storage disease. The *GALNS* gene (NM_000512.4) which is located on chromosome 16q24.3; encodes for GALNS. It is about 50 kb in length and is organized into 14 exons.[36] Heterogeneity in *GALNS* mutations are partly responsible for the extensive clinical variability of Morquio A syndrome, which can range from minimum symptoms with normal stature to the classic phenotype Evaluation of GALNS enzyme activity or identifying biallelic pathogenic variants in *GALNS* by molecular genetic testing are used to establish Morquio A syndrome. In GALNS missense, nonsense, and splicing variants, as well as small deletions, small insertions, gross insertions/duplications, and gross deletions are seen. Around 94% of variations in *GALNS* have been detected by Sequence analysis and deletion/duplication analysis identifies another 2–3%.[37] In the GALNS gene about 148 unique mutations are found to date comprising twenty six novel mutations (nineteen missense, four small deletions, one splice-site, and two insertions). Missense mutations account for 78.4% of all the studied mutant alleles; while small deletions are 9.2%; nonsense mutation are 5.0%; large deletion are 2.4%; and insertions are1.6%. Of all the stated mutations, 26.4%were attributed to transitional mutations at CpG dinucleotides.[38]

Morquio B Syndrome- β-d-Galactosidase(β-gal) is an exoglycosidase which serves as a catalyst for the hydrolysis of terminal β-linked galactose residues, insufficiency of this enzyme leads to Morquio B syndrome which is an autosomal recessive lysosomal storage disease linked to neurodegenerative disorder or dwarfism and skeletal abnormalities. Deficiency of β-gal enzyme results in buildup of β-gal substrates i.e. GM1 ganglioside and keratan sulfate. The UniProt data base accounts for about hundred gene mutations causing GM1 ganglioside and Morquio B disease.[39]

Clinical Presentation-

MPS IV first signs and symptoms appear during early childhood. Development of different skeletal abnormalities like short stature, knock knees, and deformity of the ribs, chest, spine, hips, and wrists are seen in those affected. Furthermore, they exhibit joints that are loose and very flexible (hypermobile), but some may also show restricted movement in certain joints. Odontoid process, a peglike bone in neck that stabilizes the cervical vertebrae, is underdeveloped(hypoplasia) in this condition. Hypoplasia of odontoid process can result in misalignment of the cervical vertebrae, that causes compression, damaging the spinal cord and may result in paralysis or death. (40) Short-trunk dwarfism, spondyloepiphyseal (skeletal) dysplasia and fine corneal implants are the main symptoms of Morquio syndrome. Patients with any form of Morquio syndrome continue to function with normal intelligence in contrast to other mucopolysaccharidosis diseases. While the clinical range of Morquio type A is wide, affected patients have skeletal and central nervous system abnormalities. Majority of affected individuals are normal at birth and later show growth retardation particularly short trunk and neck. A characteristic symptom seen is waddling gait with a tendency to fall. Short-trunk dwarfism, platy spondylia (flatness of the bodies of the vertebrae), hyper lordosis (exaggerated lumbar curvature of the spine), scoliosis, ovoid deformities of the vertebrae, short phalanges, metacarpal deformities and odontoid hypoplasia are the common skeletal abnormalities seen in Morquio A syndrome. Odontoid hyperplasia results in the most severe effects for patients with Morquio type A. Patients with severe type of Morquio type A often have shortened life span, not surviving past the third decade. Morquio syndrome type B was initially believed as a less severe variation of the type A disease but later it was determined that abnormality in different gene than that causing type A phenotype causes Morquio type B. Short stature due to skeletal dysplasia, pectus carinatum (protrusion of the sternum), platy spondylia, scoliosis and odontoid hypoplasia are the characteristics of Morquio type B. Morquio type B demonstrated no central nervous system involvement .[41]

Diagnosis-

Clinical suspicion is the first step in diagnosing Morquio A,]screening tests are done to confirm the diagnosis (occasionally they are excluded if there is a known family history). The gold standard for diagnosis of Morquio A according to the diagnostic algorithm is the activity assay of GALNS enzyme done in leukocytes or fibroblasts. *GALNS* gen molecular study can be used to assist in the diagnosis of Morquio A, urinary GAG analysis and/or enzyme activity analysis performed on dried blood spots are additional methods of screening for detecting Morquio A.

Urinary GAG analysis – It determines either the total accumulation of all urinary GAGs (quantitative assay) or the relative abundance of each of the GAGs (qualitative assay). It is suggested to do both quantitative and qualitative urinary GAG analyses, in Morquio A quantitative GAGs doing both quantitative and qualitative urinary GAG analyses are suggested as quantitative GAGs may not always elevated in

Morquio A and both tests are prone to false-negative results due to decreased KS excretion (relative to other GAGs) in teenagers and adults.

Enzyme assays- which are done using dried blood spot samples serve as a alternative screening tool but are not suggested for Morquio A diagnosis, due to possible challenges involving robustness and sample quality. Keratanase II-digested mono- and di-sulfated KS disaccharides can also be measured using liquid chromatography/tandem mass spectrometry, enabling concurrent determination of KS both quantitatively and qualitatively. The diagnosis of Morquio A is based on the reduced GALNS enzyme in the fibroblasts or leukocytes and wild-type activity exhibited by the control enzyme. it is furthermore essential to measure the reference enzyme to rule out any alternate diagnosis like MPS VI (caused by loss of arylsulfatase B activity), Morquio B (caused by a deficiency of β-galactosidase), multiple sulfatase deficiency (decreased activity of multiple sulfatases, including GALNS), and mucolipidoses types II/III .[42]

Treatment And Management-

Morquio A syndrome management is difficult because of its varied and progressive character and requires a multidisciplinary approach. Nevertheless, most clinicians lack knowledge regarding the unique requirements of the patients due to the rarity of the disease. This lead to creation of international guidelines for the management and treatment of Morquio A syndrome which is a result of two expert meetings conducted on August 2–3, 2013, in which an international panel of 26 specialists in paediatrics, genetics, orthopaedics, pulmonology, cardiology, and anaesthetics with experience in Morquio A assembled in Amsterdam for an expert meeting sponsored by BioMarin Pharmaceutical Inc. [43]

Enzyme replacement therapy (ERT), gene therapy, hematopoietic stem cell transplantation (HSCT), and substrate reduction therapy (SRT), are used for management of MPS, which collectively contribute the partial in improving clinical phenotypes.[44]

Enzyme replacement therapy- ERT with recombinant human GALNS (elosulfase alfa) has been approved for Morquio A syndrome, providing and offers a systemic treatment approach. Elosulfase alfa effectiveness and good safety profile have been demonstrated. ERT can help patients to lead a more active life style, enhance their mobility and endurance, it may also decrease the need for orthopedic surgery and set new standards for the future .[44] The majority of patients receiving short- term treatment of ERT have shown decrease in urine KS level nonetheless drop in blood KS level has not yet been seen. Improvement in bone pathology cannot be demonstrated by decreased urine KS level especially in short term treatment as the KS could originate from KS which is stored or filtered in kidney.[44]

Hematopoietic Stem Cell Therapy- The macrophages derived form the donor bone marrow macrophages may offer a secreting source of enzyme and access to different storage tissues, which one of the potential benefit of HSCT for MPS. The key drawback of HSCT are the adverse effects it can cause. The patients need immunosuppression and need steroid following transplantation to protect against to prevent graft-versus-host disease patients are given immunosuppression and may require steroid after transplantation. HSCT may improve growth development but shows no effect on advanced skeletal deformities. The age and the clinical condition of the recipient at transplantation, prognosis of the recipient, donor type, preparative regimen all influence the HSCT outcome. [44]

Gene Therapy- Gene therapy is an alternative approach to treat skeletal diseases, and animal research on other types of MPS is promising. The first study for Morquio A gene therapy was done

using a retrovirus vector. AAV vector is preferred since due to its vast number of benefits like long-term expression, well-characterised serotypes, wide-ranged cell and tissue tropism, low immunogenicity, and experience of preclinical and clinical trials on LSDs with clinical improvements..[44]

Anti-Inflammatory Drugs- Chronic osteoarthritis is exhibited in any major joints like hip, knee, wrist and ankle in Morquio A patients. GAG Build up causing metabolic inflammation, can be managed by either of these treatments: one is ERT, gene therapy, SRT, HSCT which reduce GAG, the alternative is to suppress secondary inflammatory processes by anti-inflammatory (or immunosuppressive) agent. These anti-inflammatories including inhibit the action of cytokines like TNF-α which is a prominent cytokine in MPS pathophysiology, blocking cell-cell interactions, and depleting certain cell types. [44]

Management of physical symptoms the primary goal of treatment of Morquio syndrome, which requires multi-disciplinary approach involving different medical specialties. [45]

Maroteaux-Lamy Syndrome

The lysosomal enzyme N-acetyl galactosamine 4-sulfatase (arylsulfatase B; ASB; EC 3.1.6.12), which catalyzes one of the steps of degradation of the glycosaminoglycans (GAGs), dermatan sulfate (DS) and chondroitin 4-sulfate (CS), is low to absent in people with mucopolysaccharidosis type VI (MPS VI), also known as Maroteaux–Lamy syndrome (MIM# 253200). As a result, these molecules gradually accumulate in lysosomes and the extracellular matrix, causing cell and tissue damage that eventually leads to a number of organ and system failures, culminating in severe clinical symptoms. MPS VI was initially described by Pierre Maroteaux and Maurice Lamy in 1963 as a unique dysostosis characterized by increased chondroitin sulfate excretion in the urine. [46]

Genetic Basis

The ARSB gene is altered (mutated) in Maroteaux-Lamy syndrome. The lysosomal enzyme arylsulfatase B is encoded by the ARSB gene. When this enzyme is deficient, the body is unable to break down glycosaminoglycans, which causes dermatan sulfate and chondroitin sulfate to build up in the cells of different tissues. It is inherited as an autosomal recessive condition caused by the ARSB mutation. The mix of alleles for a specific gene on the chromosomes inherited from the mother and father determines genetic disorders. When a person has a harmful mutation in both copies (alleles) of the gene, with one allele inherited from the mother and the other from the father, autosomal recessive genetic disorders arise. A person must inherit two mutant copies of the same gene, one from each parent, in order to suffer the illness.[47]

Clinical Presentation

At birth, people with MPS VI typically don't exhibit any symptoms of the disorder. They frequently start exhibiting MPS VI symptoms and indicators in their early years. The skeletal, cardiac, and respiratory systems are among the many body systems that are impacted by MPS VI's characteristics. [48] A huge head (macrocephaly) with an accumulation of fluid in the brain (hydrocephalus), unusual-looking facial features that are described as "coarse," and a large tongue (macroglossia) are among the skeletal abnormalities caused by MPS VI. Short stature, joint deformities (contractures) that impair movement, and dysostosis multiplex—a term used to describe a number of skeletal abnormalities visible on x-rays—are other skeletal characteristics. Many children with MPS VI develop carpal tunnel syndrome, which is typified by weakness, tingling, and numbness in the hands and fingers. MPS VI patients may experience spinal stenosis, a narrowing of the spinal canal in the neck that can compress and harm the spinal

cord. [48] Cardiac problems in people with MPS VI typically includes heart valve abnormalities. Respiratory abnormalities in this condition may involve the airway becoming narrow, which leads to frequent upper respiratory infections and short pauses in breathing during sleep (sleep apnoea). [48] An enlarged liver and spleen (hepatosplenomegaly) and a soft out-pouching around the belly button (umbilical hernia) or lower abdomen (inguinal hernia) are additional characteristics of MPS VI. Significant vision loss may result from the usual clouding of the cornea, the transparent covering of the eye. Hearing loss and repeated ear infections are also possible in people with MPS VI. In contrast to other forms of mucopolysaccharidosis, MPS VI has no effect on IQ.[48]

Diagnosis

The following is necessary for diagnosis: the examination of ASB enzyme activity in cultured skin fibroblasts or isolated leukocytes at a laboratory with accreditation to show a significant lack of ASB activity, which is indicative with MPS VI. While testing labs may have different ASB enzyme activity levels, diagnosed MPS VI patients typically have ASB activity below 10% of the lower limit of normal ASB activity. the detection of a distinct sulfatase's typical enzyme activity. The diagnosis of multiple sulfatase deficiency (MSD) is not included in this. [49]

Diagnosis is supported by the following:

i. signs of a clinical phenotype, such as small stature, hepatosplenomegaly, macrocephaly, bone-related dysostosis multiplex, inguinal or umbilical hernia, corneal clouding, or thickening of the heart valves. Newborns and patients with very modest phenotypes may not exhibit clinical phenotype.
ii. It is important to note that a pseudo-deficient MPS VI gene mutation has been reported with the patient demonstrating very low plasma ASB enzyme activity (exact level is not yet published), but normal uGAG and normal skeletal findings by X-ray supporting a normal phenotype.
iii. Demonstration of elevated total uGAG at baseline that decreases significantly within 2 to 3 months of ERT administration, conducted at the same laboratory. uGAG are elevated in the newborn period and decrease over the first year, so this sign of response to ERT may not be useful in the newborn.
iv. DS buildup and lack of CS, heparan sulfate, keratan sulfate, or hyaluronate employing high resolution electrophoresis fractionation or thin layer chromatography (TLC).
v. To support the diagnosis of carriers, an approved laboratory must demonstrate intermediate levels of leukocyte ASB enzyme activity in both parents.
vi. If the diagnosis is unclear, confirmation by ARSB gene mutational analysis should be taken into consideration. This is crucial for carrier testing or prenatal diagnosis. [49]

Treatment And Management

The goals of managing MPS VI are to improve quality of life, slow down its progression, and to prevent permanent tissue and organ damage. Early intervention may help prevent irreversible damage.[50] Maroteaux-Lamy syndrome is treated by focusing on the distinct symptoms that each person experiences. A team of specialists may need to coordinate their efforts in order to provide treatment. Treatment planning may be necessary for pediatricians, orthopedists, cardiologists, dentists, otorhinolaryngologists (ear, nose, throat specialists), pulmonologists (specialists who treat diseases of the lungs and respiratory tract), audiologists (specialists who assess and treat hearing problems), ophthalmologists (specialists who assess and treat vision problems), and other medical professionals. Genetic counselling may be of benefit for affected individuals and their families. Psychosocial support for the entire

family is essential as well. Naglazyme is an enzyme replacement therapy (ERT), a therapy in which the missing or inactive enzyme is replaced with a genetically engineered (recombinant) version. [47] Continuous positive airway pressure (CPAP), non-invasive positive pressure ventilation (NIPPV), oxygen supplementation and hypercapnia monitoring are interventions to support respiratory and sleep disorders. MPS VI is characterized by profound skeletal dysplasia with cervical spinal canal stenosis, hip abnormalities and genu valgum. Hip problems can lead to severe disability. Patients with MPS VI have progressive musculoskeletal involvement, and numerous orthopedic interventions are usually required to prevent deformity, improve function and reduce pain. [51]

SLY Syndrome-

Mucopolysaccharidosis type VII (Sly syndrome) first reported in 1973, is a rare lysosomal storage disorder occurs due to lack of enzyme β-glucuronidase, among all MPS syndrome, MPS type VII is unique typically associated with hydrops fetalis seen in newborn period. Mucopolysaccharidosis type VII (MPS VII), an autosomal recessive condition was first reported by Sly et al, the gene locus for β-glucuronidase is present on the long arm of chromosome 7 (7q21.1 -q22). Phenotypic heterogenicity is a result of the multiple mutations which have been reported. [52]

Genetic Basis

β -glucuronidase (GUS, EC 3.2.1.31; GUSB). is an enzyme responsible for the breakdown of glycosaminoglycans (GAGs), like heparan sulfate (HS), dermatan sulfate (DS), and chondroitin-4,6-sulfate (CS), lack of this enzyme causes mmucopolysaccharidosis VII (MPS VII; Sly syndrome) which is an autosomal recessive disorder The GUS gene has 12 exons, spanning 20kb and is found on chromosome 7q11.21. In individuals with MPS VII, currently about 49 distinct mutations have been reported this also includes nine novel mutations in the GUS gene. of the forty-nine mutations reported thirty-six are missense mutations, six are nonsense, two are splice site mutations, and five are deletions mutation. Out of a the103 mutant alleles was 81 (78.6%) of alleles are for missense mutations, 13 (12.6%) alleles for nonsense, 6 (5.8%) alleles for deletions, and 3(2.9%) alleles for splice-site mutations. Missense mutations are the most common among all GUS mutations. [53]

Clinical Presentation-

The clinical manifestation and course of MPS VII exhibit a wide spectrum of severity. The majority of people with MPS VII have skeletal dysplasia, hepatosplenomegaly, and cognitive disability. However, individuals with this disorder have a wide range of clinical heterogeneity, ranging from milder phenotypes with delayed start and normal or near-normal intellect to early, severe, multisystem symptoms. The first signs and symptoms that MPS VII patients exhibit with include hydrops fetalis, an umbilical or inguinal hernia, coarse facial features, hepatosplenomegaly, skeletal dysplasia, heart and respiratory issues, mental impairment, and ear infections.[54] Patients having mild or moderate manifestations have coarse facial features, corneal clouding, frequent upper respiratory infections but mild skeletal abnormalities. Short stature and greater skeletal dysplasia, macrocephaly, recurrent ear infections, gingival hypertrophy, hepatosplenomegaly, hernias and cognitive impairment are features presented in patients with more sever phenotype. The characteristic indicator of most severe form of MPS VII disease is NHIF, it is a condition in which there is excessive fluid accumulation within fetal extravascular compartments and body cavities, that is not caused by red cell alloimmunization. [54] Head, eyes, ear-nose-throat (ENT): Coarse facial feature, the predominant ocular features are corneal clouding, heavy eyebrows, visual impairment and

photosensitivity ae the primary ocular features. Most patients show ear and respiratory infections, enlarged tongue, which contribute to snoring, abnormal dentition with small and far spaced teeth, and gingival hypertrophy.(54) Lungs and heart: Reduced pulmonary function, obstructive airway disease, sleep apnea and chronic bronchitis are respiratory clinical symptoms. Valve disease and cardiomyopathies are some of the cardiac abnormalities seen. (54) Musculoskeletal: MPS VII patient survey has reported dysostosis multiplex on X-ray as the most prevalent finding. The next condition is loss of joint range of motion, resulting in reduced mobility, joint contractures and stiffness. Spine deformities included scoliosis, kyphosis and gibbus. Gneu valgum and talipes equinovarus are some of the leg deformities. Hand abnormalities included a decreased range of wrist motion, clawed hands and curved fingers. Acetabular dysplasia in hips was observed in of the patients and had hip or back pain when bending over. (54) Thoracolumbar and abdominal abnormalities: short trunk, pectus carinatum or excavatum, rib cage/chest deformities and short stature, hepatomegaly/splenomegaly and umbilical and/or inguinal hernias. (54) Neurological*:* Amongst patients with MPS VII *Limited* vocabulary and mental retardation were the most prevalent neurological symptoms. (54)

Diagnosis-

Clinical diagnosis- is dependent on characteristic manifestations of an MPS disorder, which include developmental delay and mental retardation, dysostosis multiplex, hepatosplenomegaly, and short stature. (53)

Biochemical diagnosis- The biochemical diagnosis of MPS VII is based on GUS enzyme activity quantification. the enzyme deficiency can be measured in serum, leukocytes, cultured fibroblasts, or dried blood spots (DBS) using fluorimetry with 4-methylumbelliferyl (4-MU) derived substrate and in DBS using liquid chromatography tandem mass spectrometry. GAG subclasses or GAG-derived oligosaccharides can be differentiated with precision and accuracy, and it can be employed in a variety of sample types (urine, plasma/serum, DBS, cerebrospinal fluid, cells, tissues, synovial fluid)..(55)

Molecular diagnosis- After confirmation of the biochemical diagnosis usually molecular genetics is suggested. Furthermore, it enables identification of carriers, appropriate genetic counselling for families, and prenatal genetic testing for subsequent pregnancies. p.Leu176Phe is the most prevalent variant causing MPS VII, detected in patients from different cohorts worldwide. (55)

Treatment And Management-

Early treatments for MPS VII involved of multidisciplinary management of certain symptoms and, based on the success of treatments for other MPSs, particular treatments for MPS VII were developed after considering the effectiveness of treatments for other MPSs. Present therapies include hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT) with vestronidase alfa.(56)

Enzyme replacement therapy –

US Food and Drug Administration and European Medicines Agency, authorised Vestronidase alfa ia recombinant human lysosomal β-glucuronidase employed in enzyme replacement therapy respectively, in 2017 and 2018 for the treatment of MPS VII . Vestronidase alfa, acts as an exogenous source of β-glucuronidase and breaks down accumulated GAGs when taken up into lysosomes, via the cation-independent mannose 6-phosphate receptor(56)

Hematopoietic stem cell transplantation-

The goal of HSCT id to to correct the clinical manifestations of the disease by supplying an active enzyme from the transplanted cells that can decrease substrate level .The first successful HSCT in an MPS VII patient was reported in 1998

by Yamada et al.. HSCT has previously had unpredictable outcome in MPS VII and is attributed with a significant level of risk, of rejection or death from complications. Nevertheless more recent research has suggested reversal of symptoms and clinical improvement . Due to the mixed outcomes, HSCT for patients with MPS VII should be evaluated on a case-by-case basis.(56)

Gene therapy-

Recombinant nucleic acids are used in gene therapy in order to modify genetic sequences for therapeutic purposes. It can be done in vivo – which involves administration of product directly to the patient or ex vivo in which the are modified in vitro and then transferred to the patient. MPS VII is a good candidate for gene therapy since

a) it is a monogenic disorder,
b) the deficient enzyme is soluble and can transit from an enzyme-producing cell to an enzyme-deficient cell (55)

Narowictz Syndrome

MPS IX is an extremely rare type of MPS occurs due to lack of in the lysosomal enzyme hyaluronidase, causing build up of hyaluronan. A high-molecular-weight polymer, hyaluronan is responsible for modulating cell proliferation, migration, and differentiation, extracellular water and protein homeostasis, contributes cartilage composition, 0and lubricates the joints. (56)

Genetic Basis

- Genetic mutation in the HYAL1 gene results in MPS IX.
- There are 4 known pathogenic variants within HYAL1.
- Mutations in HYAL1 and resulting enzyme deficiency leads to accumulation of the GAG hyaluronan. (57)

Clinical Presentation-

The first patient that had MPS IX was reported in 1996 with periarticular soft-tissue masses and nodular hyperplasia, a short stature, and acetabular erosions. Pertaining to the biological role of hyaluronan Skeletal and joint symptoms are frequent in MPS IX . Cysts, frequent ear infections, and a cleft palate are additional symptoms.(32)

Diagnosis-

Urinary mucopolysaccharides and oligosaccharides, lysosomal-enzyme activities. Plasma hyaluronan concentrations were determined by a 125I-labeled hyaluronan-binding-protein assay. (58) Physical examination and review of prior medical history, Peripheral smear exam may reveal abnormal lymphocytes with cytoplasmic inclusions may be observed with peripheral smears screening. X-ray of different parts of the body may reveal bony abnormalities, Genetic testing for changes in specific genes, In many cases, the diagnosis is confirmed in the lab by a test called hyaluronidase enzyme assay, performed on fibroblast cells or leukocytes.(59)

Treatment-

- Complete surgical excision is done to remove oft tissue tumors present in joints.
- Orthopaedic surgery for correcting bone and joint abnormalities
- Enzyme replacement therapy: Substitution of the absent enzyme to aid in the degradation of glycosaminoglycans
- Bone marrow transplant, if necessary
- Correction of hearing defects
- For enhancing motor abilities, special therapeutic treatment (by physical and occupational therapists) and supportive care is required

At present Research is being conducted to use gene therapy in the treatment Mucopolysaccharidosis Type IX .(60)

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