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Mucopolysaccharidosis Type II

Synonyms: Hunter Syndrome, Iduronate-2-Sulfatase Deficiency, MPS II

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Summary

Clinical characteristics

Mucopolysaccharidosis type II (MPS II; also known as Hunter syndrome) is an X-linked multisystem disorder characterized by glycosaminoglycan (GAG) accumulation. The vast majority of affected individuals are male; on rare occasion heterozygous females manifest findings. Age of onset, disease severity, and rate of progression vary significantly among affected males. In those with early progressive disease, CNS involvement (manifest primarily by progressive cognitive deterioration), progressive airway disease, and cardiac disease usually result in death in the first or second decade of life. In those with slowly progressive disease, the CNS is not (or is minimally) affected, although the effect of GAG accumulation on other organ systems may be early progressive to the same degree as in those who have progressive cognitive decline. Survival into the early adult years with normal intelligence is common in the slowly progressing form of the disease. Additional findings in both forms of MPS II include: short stature; macrocephaly with or without communicating hydrocephalus; macroglossia; hoarse voice; conductive and sensorineural hearing loss; hepatosplenomegaly; dysostosis multiplex; spinal stenosis; and carpal tunnel syndrome.

Diagnosis/testing

The diagnosis of MPS II is established in a male proband by identification of deficient iduronate 2-sulfatase (I2S) enzyme activity in white cells, fibroblasts, or plasma in the presence of normal activity of at least one other sulfatase. Detection of a hemizygous pathogenic variant in *IDS* confirms the diagnosis in a male proband with an unusual phenotype or a phenotype that does not match the results of GAG testing. The diagnosis of MPS II is usually established in a female proband with suggestive clinical features by identification of a heterozygous *IDS* pathogenic variant on molecular genetic testing.

Management

Targeted therapies: Weekly enzyme replacement therapy (ERT) with infusions of idursulfase (Elaprase®), a recombinant form of human iduronate 2-sulfatase, is approved to treat somatic manifestations and prolong

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survival. Pre-treatment with anti-inflammatory drugs or antihistamines may be needed for mild or moderate infusion reactions.

Hematopoietic stem cell transplantation (HSCT) (using umbilical cord blood or bone marrow) could provide sufficient enzyme activity to slow or stop the progression of the disease; however, no controlled clinical studies have been conducted in MPS II.

Supportive care: Interventions commonly include developmental, occupational, and physical therapy; shunting for hydrocephalus; tonsillectomy and adenoidectomy; positive pressure ventilation (CPAP or tracheostomy); carpal tunnel release; cardiac valve replacement; inguinal hernia repair; and hip replacement.

Prevention of secondary complications: Anesthesia is best administered in centers familiar with the potential complications in persons with MPS II.

Surveillance: Depends on organ system and disease severity and usually includes annual: cardiology evaluation and echocardiogram; pulmonary evaluation including pulmonary function testing; audiogram; ophthalmology examination; developmental assessment; neurologic examination. Additional studies may include: sleep study for obstructive apnea; nerve conduction velocity to assess for carpal tunnel syndrome; head/neck MRI to document ventricular size and cervicomedullary narrowing; opening pressure on lumbar puncture; and orthopedic evaluation to monitor hip disease.

Evaluation of relatives at risk: While clinical experience suggests that early diagnosis of at-risk males allows initiation of ERT before the onset of irreversible changes and often before significant disease progression, it is unclear at present whether the potential benefits of early initiation of ERT justify early diagnosis by either newborn screening or testing of at-risk male relatives.

Genetic counseling

MPS II is inherited in an X-linked manner. The risk to sibs depends on the genetic status of the mother. If the mother of the proband has the pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be carriers. Germline mosaicism has been observed. Affected males pass the pathogenic variant to all of their daughters and none of their sons. Carrier testing for at-risk female relatives and prenatal testing for pregnancies at increased risk are possible if the pathogenic variant in the family is known.

Diagnosis

The diagnosis of mucopolysaccharidosis type II (MPS II; also known as Hunter syndrome) cannot be made on clinical findings alone. The specific combination of signs and symptoms and their physical manifestation vary widely, depending on disease severity, and the evolution of individual manifestations over time is often a better indicator of a diagnosis of MPS II.

Recommendations for the diagnosis and management of MPS II have been developed by the Hunter Syndrome European Expert Council (HSEEC) using an evidence-based approach [Scarpa et al 2011].

Suggestive Findings

MPS II **should be suspected** in a male proband with the following clinical, radiographic, and laboratory findings.

Clinical features common at age 18 months to four years

- Short stature
- Hepatosplenomegaly

- Joint contractures
- Coarse facies
- Frequent ear/sinus infections
- Umbilical hernia

Radiographic findings. Skeletal survey reveals dysostosis multiplex (i.e., generalized thickening of long bones, particularly the ribs; irregular epiphyseal ossification centers in many areas; notching of the vertebral bodies).

Note: These findings may not be present in early life and are not specific to MPS II.

Laboratory findings. Urine glycosaminoglycan (GAG) analysis shows large concentrations of the GAGs dermatan sulfate and heparan sulfate.

Note: These findings are not specific to MPS II; the profile is similar to that seen in MPS I.

Establishing the Diagnosis

Male proband. The diagnosis of MPS II **is established** in a male proband by identification of absent or reduced iduronate 2-sulfatase (I2S) enzyme activity in white cells, fibroblasts, or plasma. Most affected males have no detectable activity using the artificial substrate. Detailed analytic protocols for measurement of I2S enzyme activity have been published [Johnson et al 2013]. Note: Documentation of normal enzymatic activity of at least one other sulfatase is critical, as low levels of I2S enzyme activity are present in multiple sulfatase deficiency, which can share some clinical features with MPS II.

Identification of a hemizygous *IDS* pathogenic (or likely pathogenic) variant by molecular genetic testing (see Table 1) confirms the diagnosis of MPS II in a male proband and may be useful in persons with an unusual phenotype or a phenotype that does not match the results of GAG analysis.

Female proband. Although the disease is almost exclusively reported in males, rare sporadic cases in females do occur. The diagnosis of MPS II **is usually established** in a female proband **presenting with** suggestive clinical features by identification of a heterozygous *IDS* pathogenic (or likely pathogenic) variant on molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a hemizygous or heterozygous *IDS* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of MPS II is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of MPS II has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of MPS II, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *IDS* detects missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A multigene panel** that includes *IDS* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of MPS II is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

Exome array (when clinically available) may be considered if exome sequencing is not diagnostic.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in MPS II (Hunter Syndrome)

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
IDS	Sequence analysis [3]	82% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	9%
	Complex rearrangements [7]	9%

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Single-nucleotide changes and splicing variants account for 65% of all pathogenic variants; small (i.e., intra-exon) deletions and insertions account for 17% of all pathogenic variants [Froissart et al 2007].
5. Sequence analysis may not detect complex rearrangements in males or females that result from a common pathogenic inversion between *IDS* and *IDSP1*.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Complex rearrangements result from recombination with the *IDSP1* pseudogene or from other types of processes. Testing may require multiple molecular methods (e.g., sequencing, SNP analysis, gene-targeted deletion/duplication analysis, chromosomal microarray) to confirm and map rearrangement breakpoints [Lualdi et al 2005, Froissart et al 2007, Oshima et al 2011].

Clinical Characteristics

Clinical Description

Mucopolysaccharidosis type II (MPS II; also known as Hunter syndrome) has multisystem involvement with significant variability in both age of onset and rate of progression.

CNS involvement, the most significant feature in the group of children often labeled with "early progressive" disease, manifests primarily by progressive cognitive deterioration. Such cognitive decline, combined with the progressive airway and cardiac disease, usually results in death in the first or second decade of life.

In individuals with the slowly progressive form of the disease, the CNS is minimally affected, if at all, yet the effect of glycosaminoglycan (GAG) accumulation on other organ systems may be early progressive to the same degree as in those who have progressive cognitive decline. Survival into the early adult years with normal intelligence is common in this group.

The early progressive CNS phenotype may be more than twice as prevalent as the slowly progressive form of the disease; however, accurate prevalence rates are not available. Some form of neurologic involvement is seen in 84% of affected males. Cardiovascular involvement was reported in 82% of affected individuals [Wraith et al 2008].

In individuals with MPS II, GAG accumulation occurs in virtually all organs; however, specific body systems are more affected than others.

Following are the clinical presentations of the organ systems that are earliest and most progressively affected in individuals with MPS II.

General

The appearance of newborns with MPS II is normal. Coarsening of facial features – the result of macroglossia, prominent supraorbital ridges, a broad nose, a broad nasal bridge, and deposition of GAG in the soft tissues of the face resulting in large rounded cheeks and thick lips – generally manifests between ages 18 months and four years in the early progressive form and about two years later for those with the slowly progressive form. Some develop ivory-colored skin lesions on the upper back and sides of the upper arms, pathognomonic of MPS II [Tylki-Szymańska 2014].

Growth

For most boys with MPS II growth is above average in the first five years of life, after which growth lags and short stature is the norm. Macrocephaly is universal.

Although no statistical difference is observed between height in the slowly progressive and early progressive phenotypes, the growth pattern can help in monitoring disease progression and assessing therapeutic efficacy [Patel et al 2014].

Eye

In contrast to MPS I, corneal clouding occurs occasionally and is not a typical feature of MPS II. However, discrete corneal lesions that do not affect vision may be discovered by slit lamp examination.

Optic nerve head swelling (papilledema) in the absence of increased intracranial pressure is present in approximately 20% of affected individuals and subsequent optic atrophy in approximately 11% [Collins et al 1990, Ashworth et al 2006], mainly as a result of scleral thickening due to GAG deposition.

Retinopathy has been reported most commonly in individuals with early progressive MPS II, although it can also be present in individuals with the slowly progressive form. Progressive reduction in ERG amplitude suggests deterioration in retinal function [Leung et al 1971]. Retinal degeneration leads to poor peripheral vision and night blindness, which occur frequently in individuals with MPS II, while central visual impairment due to retinal degeneration is rare [Suppiej et al 2013]. Such retinal dysfunction can be revealed by electroretinography (ERG). Visual field loss can also occur: initially, rod-mediated responses are more affected by early progression than cone-mediated responses [Caruso et al 1986]. However, signs and symptoms do not necessarily correlate with ERG change, as often only minimal changes are observed in the retinal pigment epithelium despite significant ERG changes [Ashworth et al 2006].

Other ocular findings include bilateral uveal effusions, peripheral pigment epithelial changes, and radial parafoveal folds [Ashworth et al 2006].

Ear, Nose, Throat

Common oral findings in boys with MPS II include macroglossia, hypertrophic adenoids and tonsils, and ankylosis of the temporomandibular joint, which limits opening of the mouth. These changes may be responsible for progressive swallowing impairment. GAG deposition in the larynx typically results in a characteristic hoarse voice.

Teeth are often irregularly shaped and gingival tissue is overgrown. Dentigenous cysts can occur, often causing pain and discomfort. They can be difficult to diagnose particularly in males with CNS involvement.

Conductive and sensorineural hearing loss, complicated by recurrent ear infections, occurs in most affected individuals. Otosclerosis can contribute to the conductive hearing loss. Neurosensory hearing loss can be attributed to compression of the cochlear nerve resulting from arachnoid hyperplasia, reduction in the number of spiral ganglion cells, and degeneration of hair cells.

Joints/Skeletal

Joint contractures, particularly of the phalangeal joints, are universal. The contractures cause significant loss of joint mobility and are one of the earliest noteworthy diagnostic clues.

The skeletal abnormalities in MPS II are comparable regardless of the severity of the cognitive phenotype but are not specific to MPS II. Termed "dysostosis multiplex," these radiographic findings are found in all MPS disorders and manifest as a generalized thickening of most long bones, particularly the ribs, with irregular epiphyseal ossification centers in many areas. Notching of the vertebral bodies is common.

Hip dysplasia is the most common long-term orthopedic problem and can become a significant disability with early-onset arthritis if not treated.

Respiratory

Frequent upper-respiratory infections are one of the earliest findings in MPS II. The airway progressively narrows as GAGs accumulate in the tongue, soft tissue of the oropharynx, and the trachea, eventually leading to airway obstruction. Complicating this obstruction are thickening of respiratory secretions, stiffness of the chest wall, and hepatosplenomegaly, which can reduce thoracic volume. The progression of airway obstruction is relentless and usually results in sleep apnea and the need for positive pressure assistance and eventually tracheostomy.

Cardiovascular

The heart is abnormal in the majority of boys with MPS II and is a major cause of morbidity and mortality; 82% of individuals have cardiovascular signs/symptoms, 62% have a murmur that can be related to valvular disease,

including (in order of frequency) the mitral, aortic, tricuspid, and pulmonary valves. Cardiomyopathy, hypertension, rhythm disorder, and peripheral vascular disease are seen occasionally (<10%) [Wraith et al 2008].

Gastrointestinal

Hepatomegaly and/or splenomegaly occur in most affected individuals. Umbilical/inguinal hernia is also a frequent finding. In persons with early progressive MPS II, chronic diarrhea is a common complaint.

Nervous System

Infants with MPS II appear normal at birth; early developmental milestones may also be within the normal range. Delay in global developmental milestones is typically the first indication of brain involvement in children with the CNS form of MPS II. Presence of sleep disturbance, increased activity, behavior difficulties, seizure-like behavior, perseverative chewing behavior, and inability to achieve bowel and bladder training may be strongly correlated with subsequent cognitive dysfunction [Holt et al 2011].

As is the case for the other organ systems, progression of the CNS manifestations is inexorable, usually resulting in developmental regression between ages six and eight years.

The most common neurologic signs are behavioral and cognitive problems, which Wraith et al [2008] found in 36% and 37% of affected individuals, respectively. Behavioral problems occur in both the early progressive and slowly progressive forms of the disease [Young & Harper 1981, Wraith et al 2008] but are more common in the early progressive form.

Chronic communicating hydrocephalus may complicate the clinical picture, especially on the background of deteriorating cognitive ability. Seizures may also occur.

The decline of cognitive function, combined with progression of early progressive pulmonary and cardiac disease, generally heralds the terminal phase of the disease, with death in the first or second decade of life.

Males who do not have the progressive CNS form of the disease have normal or near-normal intelligence. However, while deteriorating cognitive abilities and seizures are not common in males with the slowly progressive form of MPS II, chronic communicating hydrocephalus may still occur.

Carpal tunnel syndrome (CTS) is often an overlooked complication of MPS II. Unlike adults with CTS, most children with MPS II do not complain of the typical symptoms. Nonetheless, nerve conduction studies are abnormal. Hand function improves after surgical correction.

Another nervous system complication that must be monitored is narrowing of the spinal canal (spinal stenosis), particularly in the cervical region, with spinal cord compression.

Endocrine

Infants with MPS II appear normal at birth; in the first years of life the height of most children with MPS II is above the 50th percentile and in some it is over the 97th percentile. However, growth velocity decreases with age. By age eight years, height is below the third percentile, and nearly all children exhibit growth restriction before puberty [Schulze-Frenking et al 2011]. The cause of short stature is unknown; it may be related to osseous growth-plate disturbances.

Genotype-Phenotype Correlations

Limited information is available regarding genotype-phenotype correlations:

- The pathogenic variant c.1122C>T (which creates a new donor splice site at exon 8 with the loss of 20 amino acids) is primarily associated with the slowly progressive phenotype [Muenzer et al 2009].

- Males with complete absence of functional enzyme as a result of gene deletion or complex gene rearrangements (~17% of affected individuals) invariably manifest the early progressive CNS presentation of the disease [Wraith et al 2008].
- Recent data from a cohort study of Dutch individuals with MPS II suggest that very low or cell-type-specific IDS residual activity is sufficient to prevent the neuronal phenotype of MPS II. While the molecular effects of *IDS* pathogenic variants do not discriminate between MPS II phenotypes, the IDS genotype is indicated as a strong predictor [Vollebregt et al 2017].

Penetrance

Penetrance of MPS II in males is 100%; however, it is anticipated that if newborn screening becomes available for MPS II, much milder presentations would be documented.

Nomenclature

The modifier terms "mild/attenuated" and "severe" were often used in the past to describe the phenotypic variability of the condition, but it is clear (as for all MPS disorders) that the range of severity is wide. It is now considered inappropriate to use these terms since the disease significantly alters the quality of life. Thus, the terms "slowly progressive" (to describe the former "attenuated" form of the disease) and "early progressive" (to describe the form of the disease previously designated "severe") are currently being considered to better reflect the continuum of disease severity.

Prevalence

Several surveys suggest an incidence between 1:100,000 and 1:170,000 male births [Nelson et al 2003, Baehner et al 2005].

Genetically Related (Allelic) Disorders

Deletions extending beyond the *IDS* locus result in symptoms atypical of MPS II. These deletions cause an earlier progressive central nervous system phenotype and may be associated with other atypical features such as ptosis and seizures [Probst et al 2007].

Differential Diagnosis

The differential diagnosis for mucopolysaccharidosis type II (MPS II, or Hunter syndrome) essentially includes all of the other MPS disorders, given the significant overlap of clinical presentation and radiologic findings (see MPS I).

Multiple sulfatase deficiency, mucolipidosis type II and type III alpha/beta (see *GNPTAB*-Related Disorders), and mucolipidosis type III gamma may also present with findings similar to MPS II.

See Mucopolysaccaridoses: OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.

Management

Management guidelines for individuals with mucopolysaccharidosis type II (MPS II) have been published [Scarpa et al 2011].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with MPS II, the following evaluations are recommended if they have not already been completed:

- Echocardiogram
- Pulmonary function testing preferably in individuals age six years and older. Pulmonary function testing (e.g., spirometry) can be quite challenging in younger individuals and may be impossible for individuals with significant central nervous system (CNS) involvement since it requires their full cooperation and is effort dependent [Kamin 2008].
- Sleep study if sleep apnea is a potential concern or in case of sleep disturbances not related to upper airway obstruction or impairment of ventilatory control (e.g., difficulty initiating or maintaining sleep, awakening several times per night, decreased REM sleep, atypical sleep stage distribution, and restless legs), which might start to manifest at a median age of four to five years [Rapoport & Mitchell 2017]
- Audiologic evaluation
- Nerve conduction velocity (NCV) and nerve ultrasound examination to assess for carpal tunnel syndrome
- Head-cervical MRI and/or opening pressure on lumbar puncture to assess for hydrocephalus and spinal cord compression. Because MRI needs to be performed under sedation and/or intubation in individuals with the early progressive form, there is an increased risk of compromising the upper airway. See Prevention of Secondary Complications.
- Ophthalmologic evaluation
- Developmental assessment
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

There is no cure for MPS II.

Targeted Therapies

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Table 2. Mucopolysaccharidosis Type II: Targeted Treatment

Targeted Treatment	Dosage	Benefits	Considerations
Idursulfase (Elaprase®) enzyme replacement therapy (ERT) [1]	Intravenous weekly dose of 0.5 mg/kg [2, 3]	• Survival in idursulfase-treated persons is higher than in those who are untreated. [4] • Idursulfase has positive effects on functional capacity (distance walked in 6 mins & forced vital capacity), liver & spleen volumes, & urine GAG excretion. [5] • ERT improves somatic signs & symptoms of disease in all persons, incl infants age <1 year & persons w/early progressive MPS II phenotype. [6]	• Long-term use of ERT is similarly effective in young (age 1.6-12 years at start of ERT) & older persons (age 12-27 years at start of ERT). [7] • Since idursulfase does not cross blood-brain barrier, no effect on CNS disease is anticipated. [8] • Infusion-related reactions are comparable to similar reactions seen w/other ERT products. [2, 9, 10]

CNS = central nervous system; GAG = glycosaminoglycan

1. A recombinant form of human iduronate 2-sulfatase that has been approved in the United States and the European Union

2. Pre-treatment with anti-inflammatory drugs or antihistamines, as is often done for enzyme replacement therapy (ERT) in other conditions, is not suggested on the label for Elaprase®; however, if mild or moderate infusion reactions (e.g., dyspnea, urticaria, or systolic blood pressure changes of ≤20 mm Hg) cannot be ameliorated by slowing the infusion rate, the addition of treatment one hour before infusion with diphenhydramine and acetaminophen (or ibuprofen) to the regimen usually resolves the problem. Pre-treatment can typically be discontinued after six to ten weeks.

3. Severe non-allergic anaphylactoid reactions such as major changes in blood pressure, wheezing, stridor, rigors, or drop in oxygen saturations should be immediately addressed by stopping the infusion and giving appropriate doses of subcutaneous epinephrine, intravenous (IV) diphenhydramine, and hydrocortisone or methylpredinsolone. Subsequent infusions should then be given at a significantly reduced rate with pre-treatment with prednisone 24 hours and eight hours before the infusion, diphenhydramine and acetaminophen or ibuprofen orally one hour before the infusion, and IV methylpredinsolone just before beginning the infusion.

4. Burton et al [2017]

5. da Silva et al [2016], Muenzer et al [2017]

6. Lampe et al [2014a], Lampe et al [2014b]

7. Tomanin et al [2014], Muenzer et al [2017]

8. In order to overcome the limitations in the treatment of the central nervous system (CNS), intrathecal ERT and gene therapy are currently under investigation as future therapies [Motas et al 2016, Stapleton et al 2017]. Shire recently sponsored a Phase II/III clinical trial examining the use of intrathecal iduronate 2-sulfatase in young individuals with MPS II with CNS involvement (NCT02055118).

9. The etiology of the more severe forms of these non-allergic reactions, referred to as anaphylactoid, is unknown. Current evidence suggests that anaphylactoid (as opposed to anaphylactic) reactions are not immune mediated [Mayer & Young 2006].

10. Infusion reactions are generally mild and include brief, insignificant decreases or increases in heart rate, blood pressure, or respiratory rate; itching; rash; flushing; and headache. Mild reactions can usually be managed by slowing the infusion rate for several treatments and then slowly returning to the prior rate.

Hematopoietic stem cell transplantation (HSCT) using umbilical cord blood or bone marrow is a potential way of providing sufficient enzyme activity to slow or stop the progression of the disease [Guffon et al 2009, Annibali et al 2013]; however, the use of HSCT is controversial because of the associated high risk of morbidity and mortality. Furthermore, it remains unclear if treatment early in life significantly reduces the progression of neurologic disease [Mullen et al 2000], and anecdotal case reports published to date have been disappointing, quite unlike the reports of bone marrow transplantation (BMT) in Hurler syndrome (MPS I). Overall, the efficacy of BMT for MPS II cannot be determined until a number of children with MPS II younger than age two years with known or probable severe CNS disease undergo transplantation [Tanaka et al 2012]. A recent single report of seven-year follow up of a prenatally diagnosed boy with MPS II who received HSCT with umbilical cord blood cells at age 70 days suggest that cognitive skills were preserved [Barth et al 2017]. It has been shown that HSCT and ERT have equal efficacy in restoring growth in children with MPS II; both treatments are limited

by age of the affected individual and disease progression (e.g., neurologic and heart impairment) at the start of treatment [Patel et al 2014]. Nevertheless, the use of HSCT has been controversial because of limited information regarding the long-term outcomes and the associated high risk of morbidity and mortality. Until two decades ago, HSCT had high mortality rates because of (1) the preconditioning regimen prior to HSCT, which caused severe side effects including increased susceptibility to infection and (2) poor donor selection, which resulted in a high risk of graft-vs-host disease [Stapleton et al 2017]. With the development of new conditioning protocols and the creation of bone marrow donor registries and umbilical cord banks, HSCT has become more accessible [Barth et al 2017]. Although further studies are required, HSCT should continue to be considered as a treatment option particularly because of its lower cost (compared to lifelong ERT treatment) and potential for improving quality of life for affected individuals and their families [Barth et al 2017].

Supportive Care

The involvement of specialists for each affected organ system is required to monitor and treat specific problems (see Clinical Description). Commonly required interventions include the following:

- Developmental, occupational, and physical therapy
- Shunting for hydrocephalus
- Tonsillectomy and adenoidectomy
- Positive pressure ventilation (CPAP or tracheostomy)
- Carpal tunnel release
- Cardiac valve replacement
- Inguinal hernia repair
- Hip replacement

Prevention of Secondary Complications

Given the risks associated with sedation with/without intubation, anesthesia is best administered in centers familiar with the potential complications in persons with MPS II. Risks associated with general anesthesia include the following:

- Ankylosis of the temporomandibular joint can restrict oral access to the airway.
- Visualization of the vocal cords is compromised by the large tongue, GAG-infiltrated soft tissues, and large tonsils and adenoids.
- Care must be taken to avoid hyperextension of the neck secondary to atlantoaxial instability and cervicomedullary compression that may be present.

Nasopharyngeal intubation is often necessary. When endotracheal intubation is difficult or when sedation is required for brief procedures, laryngeal mask airway may be indicated.

The risk of airway complications may continue following successful surgery. Extubation may be difficult because laryngeal edema, which has been reported up to 27 hours post surgery, may prevent maintenance of a proper airway [Hopkins et al 1973]. Breathing a helium-oxygen mixture during extubation has been reported to relieve obstruction and improve outcome [McGarvey & Pollack 2008].

Surveillance

Guidelines for surveillance have been developed [Scarpa et al 2011].

Modes of surveillance for complications over time depend, like treatment, on organ system and disease severity. Because all persons with MPS II face the same organ failure issues, with the time of failure being dependent on severity, when and how often to monitor for change cannot be generalized. However, the following studies/evaluations are likely indicated on at least a yearly basis beginning in early to mid-childhood:

- Cardiology visit with echocardiogram
- Pulmonary clinic visit with pulmonary function testing
- Audiogram
- Ophthalmology examination, including examination through a dilated pupil to view the optic disc
- Developmental assessment
- Neurologic examination

The following are appropriate at baseline and/or when symptoms/age dictates:

- Sleep study for obstructive sleep apnea
- NCV study for evidence of carpal tunnel syndrome
- Head/neck MRI to document ventricular size and cervicomedullary narrowing
- Opening pressure on lumbar puncture
- Orthopedic evaluation to monitor hip disease

Evaluation of Relatives at Risk

Although clinical experience suggests that early diagnosis of at-risk males allows initiation of ERT before the onset of irreversible changes and often before significant disease progression [Muenzer 2014], a recent study showed that while early diagnosis and use of ERT improved outcomes, mortality and morbidity remained high [Franco et al 2017]. It is still unclear whether early diagnosis (either by newborn screening or testing of at-risk male relatives) is beneficial as no data are available on whether early ERT improves the outcome of the somatic disease in MPS II. ERT is not expected to benefit children with the CNS form of the disease.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

A number of interventions are being evaluated for potential use in MPS II.

A Phase II/III study of intrathecal delivery of iduronate 2-sulfatase has been initiated (NCT02055118). Preliminary results showed no toxicity of the protein injected intrathecally at the dosage used (10 mg and 30 mg). The GAG concentration in the CSF was significantly reduced but clinical efficacy needed further evaluation [Muenzer et al 2014].

Another ongoing multicenter study is evaluating the effect of a one-year course of monthly intrathecal administration of 10 mg of idursulfase on neurodevelopmental status in children with MPS II and cognitive impairment who have previously received and tolerated a minimum of four months of Elaprase® therapy.

Other therapies under preclinical investigation include more direct delivery of enzyme into the CNS, higher peripheral dosing regimens, small-molecule therapies such as chaperone and substrate reduction, and gene therapy [Beck 2010]. Tissue uptake (including the brain and spinal cord) via the transferrin receptor of a fusion protein between iduronate 2-sulfatase (I2S) and a monoclonal antibody against the mouse transferrin receptor is being studied [Zhou et al 2012].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic

status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Mucopolysaccharidosis type II (MPS II; also known as Hunter syndrome) is inherited in an X-linked manner.

Risk to Family Members

Parents of a proband

- The father of an affected male will not have the disease nor will he be hemizygous for the *IDS* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one affected child and no other affected relatives and if the *IDS* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism (germline mosaicism has been observed in MPS II) [Froissart et al 2007].
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote (carrier) or the affected male may have a *de novo IDS* pathogenic variant, in which case the mother is not a carrier.
- On rare occasion, heterozygous females manifest findings of MPS II. This is thought to result from skewed inactivation of the normal paternally inherited X chromosome and expression of the maternally inherited mutated *IDS* allele [Jurecka et al 2012, Guillén-Navarro et al 2013].

Sibs of a proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has the *IDS* pathogenic variant identified in her son, the chance of transmitting it in each pregnancy is 50%. Males who inherit the *IDS* pathogenic variant will be affected; females who inherit the *IDS* pathogenic variant will be carriers (on rare occasion, heterozygous females manifest findings of MPS II).
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *IDS* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the general population because of the possibility of maternal germline mosaicism (germline mosaicism for an *IDS* pathogenic variant has been observed in MPS I) [Froissart et al 2007].

Offspring of a proband. Affected males transmit the pathogenic variant to:

- All of their daughters, who will be (heterozygotes) carriers and will usually not be affected;
- None of their sons.

Other family members. The proband's maternal aunts may be at risk of being heterozygotes (carriers) for the *IDS* pathogenic variant, and the aunts' offspring, depending on their sex, may be at risk of being heterozygotes (carriers) for the pathogenic variant or of being affected.

Heterozygote (Carrier) Detection

Molecular genetic testing. Carrier testing for at-risk female relatives requires **one** of the following:

- Testing for the family-specific *IDS* pathogenic variant identified in an affected male relative, OR
- If an affected male is not available for testing, molecular genetic testing:
  1. First by sequence analysis
  2. If no *IDS* pathogenic variant is identified, use of gene-targeted deletion/duplication analysis methods to detect intragenic and exon deletions

3. If no *IDS* pathogenic variant is identified, use of appropriate molecular methods to detect complex rearrangements from recombination between *IDS* and the pseudogene, *IDSP1*, or other processes

Biochemical genetic testing. Measurement of iduronate 2-sulfatase enzyme activity is not reliable for detection of heterozygous females as a carrier may have normal I2S enzyme activity resulting from X-chromosome inactivation that may be non-random.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on testing at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *IDS* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. In families in which the causative *IDS* pathogenic variant has been identified, prenatal testing should be performed by molecular genetic testing, as assay of I2S enzyme activity is more difficult.

Biochemical genetic testing. Prenatal testing is technically feasible for pregnancies at increased risk for MPS II by measuring I2S enzyme activity in cultured cells obtained by amniocentesis usually performed at approximately 15 to 18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. However, such testing is not readily available. (Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.)

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Canadian Society for Mucopolysaccharide and Related Diseases**
  Canada
  Phone: 800-667-1846
  Email: info@mpssociety.ca
  www.mpssociety.ca
- **Medline Plus**
  Mucopolysaccharidosis type II
- **MPS Society**

United Kingdom
Phone: 0345 389 9901
Email: mps@mpssociety.org.uk
www.mpssociety.org.uk

- **National MPS Society**
  Phone: 877-MPS-1001
  www.mpssociety.org
- **National Organization for Rare Disorders (NORD)**
  Phone: 800-999-6673
  Patient Assistance Programs
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  www.newbornscreening.hrsa.gov/your-state

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Mucopolysaccharidosis Type II: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
IDS	Xq28	Iduronate 2-sulfatase	IDS @ LOVD	IDS	IDS

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Mucopolysaccharidosis Type II (View All in OMIM)

300823	IDURONATE 2-SULFATASE; IDS
309900	MUCOPOLYSACCHARIDOSIS, TYPE II; MPS2

Gene structure. *IDS* consists of nine exons and spans about 24 kb of genomic DNA. An *IDS* pseudogene, *IDSP1*, is located about 25 kb telomeric to *IDS*. Homologous regions shared by *IDS* and *IDSP1* predispose to unequal recombination events, leading to complex rearrangements and sometimes large deletions. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 300 *IDS* pathogenic variants have been described, the majority being single-nucleotide variants or small deletions [Froissart et al 2007]. Novel pathogenic variants are being identified continuously [Brusius-Facchin et al 2014]. Up to 18% of MPS II results from deletion of one or more exons or the whole gene, and/or complex rearrangements, typically associated with the early progressive phenotype.

Lack of genotype/phenotype correlation is demonstrated by identification of several pathogenic missense variants (p.Arg468Gln, p.Arg468Trp, and p.Ser333Leu) in individuals with the early progressive phenotype and others with the intermediate or slowly progressive phenotype. At least two sibships of one brother with the early progressive phenotype and another brother with a slowly progressive phenotype have been reported [Yatziv et al 1977].

- Missense variants make up the majority of IDS pathogenic variants, resulting in reduced expression of I2S enzyme activity and variable disease severity. Genotype-phenotype predictions are not reliable in these cases.

- In males with large deletions and intragenic rearrangements, no enzyme is produced and these individuals typically have the early progressive phenotype (see Genotype Phenotype Correlations).

A 178-bp deletion in the promoter region was identified in two affected individuals with low enzyme activity [Brusius-Facchin et al 2013]. Alteration of the promoter region may explain low enzyme activity in some affected individuals in whom no *IDS* pathogenic variant in the coding region or (multi)exon or whole-gene deletion was detected.

Table 3. *IDS* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.998C>T	p.Ser333Leu	NM_000202.5 NP_000193.1
c.1403G>A	p.Arg468Gln	
c.1402C>T	p.Arg468Tryp	
c.1122C>T	Splice variant	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. Iduronate 2-sulfatase (I2S), a 550-amino-acid protein, catalyzes the release of sulfate from the iduronate sulfate residues of heparan sulfate and dermatan sulfate [Neufeld & Muenzer 2015].

Abnormal gene product. Pathogenic variants in *IDS* result in absence or reduced levels of I2S enzyme activity, which decreases the amount of the sulfate moiety released from the glycosaminoglycans (GAGs) dermatan sulfate and heparan sulfate during their degradation, disrupting cellular function and causing disease.

Chapter Notes

Author Notes

Dr Maurizio Scarpa is the Director of the Center for Rare Diseases at the Horst Schmidt Klinik in Wiesbaden, Germany. He is also the President of the Brains for Brain Foundation (B4B). B4B aims to develop new and innovative therapeutic strategies to cross the blood-brain barrier and supports the following activities in the field of rare neurologic disorders: scientific research, knowledge dissemination, social and socio-medical assistance, and health assistance.

Author History

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Maurizio Scarpa, MD, PhD (2011-present)

Revision History

- 11 April 2024 (aa) Revision: targeted therapies linked as Key Section
- 4 October 2018 (sw) Comprehensive update posted live
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