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CLINICAL FINDINGS, DIAGNOSIS AND TREATMENT STRATEGIES OF MUCOPOLYSACCHARIDOSIS TYPE I

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ABSTRACT

Mucopolysaccharidosis type I (MPS I) is a disease caused by the deficiency of alpha-L-iduronidase (a lysosomal enzyme), as a result of which glycosaminoglycans accumulate resulting in progressive multi-organ dysfunction. Cases of MPS I are classified into severe and attenuated forms. Hurler syndrome is the severe form and Hurler-Scheie and Scheie syndromes are the attenuated forms. It has broad clinical spectrum which differs in both severe and attenuated phenotypes. It is a rare disease. One case is seen in one lac births. Its diagnosis is established by clinical and laboratory findings, molecular gene testing and detecting the deficiency of alpha-L-iduronidase. Two treatment options i.e. hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT) are available. Disease management of MPS I is not consistent because of heterogenous phenotypes, few therapeutic options and rarity. Information about the history of MPS I may aid in the management of affected individuals.

KEYWORDS: Mucopolysaccharidosis type I, Hematopoeitic stem cell treatment, Enzyme replacement therapy.

INTRODUCTION

Mucopolysaccharidoses are a group of rare diseases caused by the absence or deficiency of lysosomal enzymes which are required for breaking glycosaminoglycans (formerly called mucopolysaccharides). Glycosaminoglycans are long chains of carbohydrates that occur in the fluids that lubricate joints and are also found in cells. In mucopolysaccharidosis, these molecules collect in the cells, connective tissues and blood resulting in damage of cells due to which physical appearance, mental abilities and system functioning is affected.

Mucopolysaccharidosis type I (MPS I) is caused by the deficiency of alpha-L-iduronidase, due to which degradation of glycosaminoglycans dermatan sulfate and heparan sulfate do not occur. It is an autosomal recessive disease. MPS I shows clinical variability in age of onset as well as in rate of progression. Cases are classified into severe and attenuated forms. Severe form (Hurler syndrome) is well described and represents the majority of known cases. It can be delineated accurately. Patients usually die, as a result of progressive neurologic disease and cardiorespiratory failure, within the first decade. Attenuated form (Scheie and Hurler-Scheie syndromes) cases vary due to age of onset, symptoms and course of disease. Disabilities attributable to somatic involvement are observed in patients. These patients survive into adulthood. Incidence of MPS I, a panethnic disorder, is 1 case per 1,00,000 live births. Of the total MPS I, severe phenotypes represent ~50% to 80% while attenuated phenotypes represent ~26%.[1]

Genetic aspects

Mutational heterogeneity of MPS I underlies the clinical heterogeneity. The type of mutation determines the phenotype. The predictive value of genotype for many patients is limited because of the large number of private (single-occurrence) mutations. In the Human Gene Mutation Database, 110 mutations in alpha-L-iduronidase that are associated with MPI are listed. The majority of mutations are small deletions, misense mutations and nonsense mutations. Among these, Q70X and W402X, null alleles are present in individuals with severe phenotype. Besides these, R89W and R89Q are present in patients with attenuated phenotype.[2] Severity of disease cannot be predicted by molecular tests as detection of small differences in the activity of enzyme is difficult. Therefore, to precisely classify the disease certain factors i.e. presence of null mutations, age of onset and clinical characteristics are important.[3]

Clinical Findings

Symptoms and signs

Facial features coarseness, macrocephaly, scaphocephaly, and thickening of the lips, tongue and alae nasi are

observed in individuals with severe MPS I while in attenuated type, facial features coarseness is less obvious and individuals have square jaw, wide mouth, short neck and micrognathia alongwith growth retardation. Progressive hepatosplenomegaly causing protuberance of the abdomen is common. Moderate to severe hearing loss is common and is related to the somatic disease severity. Persistent copious nasal discharge and chronic recurrent rhinitis are common. CNS involvement and obstructive airway disease and cause sleep apnea. Individuals have deep and gravelly voice. All patients with severe phenotype have cardiovascular disease. Mitral and aortic regurgitotion results from progressive stiffening and thickening of the valve leaflets. One of the leading causes of premature death in individuals with MPS I is cardiac involvement and respiratory complications.[23]

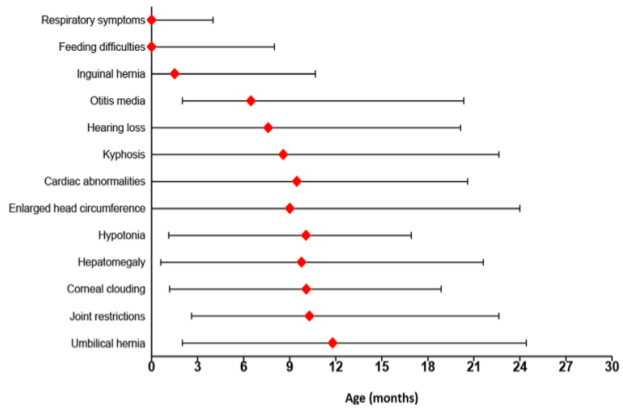

Figure 1: Median age of symptom onset with minimum to 9th decile range.

All individuals with severe MPS I has dysostosis multiplex (progressive skeletal dysplasia) involving all bones and more than 85% of patients with attenuated phenotype have dysostosis.[4] All individuals having severe MPS I and approximately 82% of individuals with attenuated MPS I exhibit corneal clouding which can cause visual disability, opic atrophy, glaucoma and retinal degeneration. Inguinal hernias and umbilical hernias are present. The risk of communicating high pressure hydrocephalus is greater in severe MPS I. Intellect may be normal or nearly normal in attenuated MPS I but a decline in intellect occurs monthly thereafter in severe MPS I. Symptom onset timing of 55 patients is shown graphically in Figure 1.

Laboratory findings

A clinical suspicion of MPS requires the determination of urinary glycosaminoglycans concentration. In all types of MPS, these concentrations are elevated. In a patient with a suggestive clinical picture, diagnosis cannot be ruled out due to the normal levels of GAG. Various methods can be used to measure urinary GAG concentrations. Analysis of urinary GAG levels may be qualitative (Analyzing the specific GAGs excreted by electrophoresis) or quantitative (measuring the total urinary uronic acid). Specific lysosomal enzyme deficiency, including MPS I, cannot be diagnosed by either qualitative or quantitative method; however, the likely presence of an MPS disorder is indicated by an abnormality that can be detected by either or both methods. Quantification with dimethylmethylene blue is one of the recommended tests. Elevated levels of GAG are present in individuals with MPS I. In normal individuals, urinary GAG excretion is more at birth and decreases rapidly afterwards;[5] the concentration no longer changes after the age of 21 years. Therefore, reference standards should be used for interpretation of results. The type of GAG present in excess can be identified by electrophoresis or chromatography, which helps in identifying enzymes.[6] GAG electrophoresis include and exclude certain MPS disorders; however, additional testing is required for definitive diagnosis. Urinary GAG measurement is a not a specific screening test. Both quantitative and qualitative methods have low sensitivity if the urine is too dilute, as false negative results may occur.

Diagnosis

Lack of disease awareness and symptom variability in MPS I result in delayed diagnosis. The diagnosis of MPS I is established by clinical and laboratory findings explained above, molecular gene testing for identifying a biallelic pathogenic variant and detecting the deficiency of lysosomal enzyme alpha-L-iduronidase. A professional having experience in lysosomal storage disorders should review any diagnostic test because not only the assays are complex but also the interpretation of results is difficult.[7]

Evaluations Following Initial Diagnosis

The extent of disease in patient with MPS I, can be established by evaluations following initial diagnosis. Hearing assessment, developmental assessment, peripheral nerve involvement and spinal cord assessment, ENT assessment and ventilating tubes consideration for recurrent otitis media, cardiac evaluation with echocardiography for ventricular function and size assessment are recommended. Degree and extent of joint involvement and spine involvement is determined by skeletal survey. Ophthalmologic examination is done for measuring intraocular pressure and visual acuity. Slit lamp examination of the cornea, and visual field testing and electroretinography for retinal function assessment are performed. Cranial imaging, including assessment of possible hydrocephalus, is done by MRI. A genetic counselor and/or a clinical geneticist is consulted. Condition of the patient can be evaluated by the assessments presented in Table 1.

Table 1: Minimum program of assessments for clinical follow up of patients with MPS I.

	Initial assessment	Every 6-month	Annual	Bi-annual
General				
General data	X			
Diagnosis	X			
Medical history	X	X		
Physical examination	X	X		
General aspect	X	X		
Clinical assessments				
Neurological/CNS				
Cranial MRN	X			X
Spine MRN	X			X
Ophthalmologic				
Visual acuity	X		X	
Retina assessment	X		X	
Cornea assessment	X		X	
Auditory				
Audiometry	X		X	
Cardiac				
Echocardiogram	X			X
Electrocardiogram	X			X
Respiratory				
FVC/FEV1	X	X		
Sleep study	X		X	
Gastrointestinal				
Volume of spleen	X			X
Volume of liver	X			X
Musculoskeletal				
Bone inventory with radiography	X			X
Biometry and laboratory examinations				
Height/Weight	X	X		
Cephalic perimeter	X	X		
Arterial pressure	X	X		
Enzymatic activity	X			
Urinary GAGs	X	X		
Urine I	X	X		
Health condition assessment				
MPS health condition assessment questionnaire	X	X		

Molecular genetic testing

Single-gene testing and use of a multi-gene panel are included in molecular testing approaches. Summary of molecular genetic testing is given in Table 2. In single-gene testing, first of all IDUA sequence analysis is performed and then gene-targeted duplication/deletion analysis is performed, if only one or no pathogenic variant is found. The usefulness of such testing is unknown as no whole-IDUA or exon duplication or deletion cause MPS I. In multi-gene panel, IDUA is considered along with other genes. The genes of interest and sensitivity of diagnosis vary. Some genes not associated with the conditions of MPS I may be included in multi-gene panels as clinicians determine which multi-gene panel provides the best opportunity, at the most reasonable cost, to identify the altered gene. Sequence analysis is used to detect benign, likely benign, pathogenic or likely pathogenic variants. [8]

Table 2: Summary of molecular genetic testing used in MPS I.

Gene	Test method	Proportion of probands with pathogenic variants detectable by this method
IDUA	Sequence analysis	95%-97%
	Gene-targeted deletion/duplication analysis	None reported

Alpha-L-iduronidase enzyme activity

A definitive diagnosis of MPS I is based on the deficient activity of alpha-L-iduronidase in tissues; typically, plasma, peripheral blood leukocytes, or fibroblasts. Studies conducted using fibroblasts from patients with MPS I showed that mild phenotype can be produced by only 0.13% of normal alpha-L-iduronidase activity.[9]

Genetic counseling and prenatal diagnosis

For predicting the phenotype, for aiding in prenatal diagnosis and for allowing genetic counseling identification of the genotype is important. Therefore, DNA is obtained from blood, saliva, oral mucosa cells or other materials of the patient and/or a family member. Either DNA testing (for patient's family members when

mutations are known) or enzyme testing can be used for prenatal diagnosis. In families having prior history of MPS, further cases can be detected by prenatal diagnosis; by collecting amniotic fluid in the first or second trimester of pregnancy or by means of chorionic villus biopsy. Diagnosis is based on the enzyme activity in the cells. Umbilical cord blood can be used for enzymatic diagnosis. This diagnosis may be quickly performed if mutations are already known in the family. The recurrences of MPS I can be prevented by genetic counseling as it provides information of reproductive risks. The risk of recurrence is 25% for each new pregnancy for a normal couple with a child having MPS I. Parental consanguinity is often present as in most autosomal recessive diseases.[24]

Differential diagnosis

The findings in patients of MPS I overlap those of other lysosomal storage diseases e.g. MPS type II and IVA, multiple sulfatase deficiency, alpha-mannosidosis, mucolipidosis type I, II and III. They can be distinguished by clinical findings or biochemical testing. In mucolipidosis type II and III, deficiency in alpha-L-iduronidase activity is observed. In these conditions, alpha-L-iduronidase is not transported to the lysosome although it is synthesized in adequate amounts. MPS I is considered in the differential diagnosis of juvenile idiopathic arthritis as non-inflammatory arthritis may be presented at any age by patients with attenuated MPS I.[10]

Treatment

Psychological assessment and follow-up

The patients as well as caregivers may experience anguish, pain, fear and anxiety. The process of accepting this disease develops in several stages including anger, fear of being cheated, anxiety and depression. The emotional adaptation of a patient's family is important in determining the psychological state of a patient. Family disarrangement often leads to hamper the diagnosis and the treatment. A psychologist must play an important role helping the family in this difficult situation and should convince the caregivers or parents to follow the treatment. There will be numerous mental, behavioral and cognitive assessments of the patient and parents and health professionals should be informed about the results of this assessment so they can closely monitor the impairments resulting from the disease. The reassessment of the intellectual level of pre-school aged child must be performed after every 7 months. In addition to the psychological support, educational and medical support must be given to the patient. The social support networks may prove useful in providing access to the information and services including medicines.

Hydrotherapy

Hydrotherapy, also called as aquatic rehabilitation can be quite helpful for the children suffering from MPS because it is playful as well as stimulating. Water provides buoyancy which helps alleviate some muscle disorders because movement combined with some exercises strengthen weaker muscles. Buoyancy of water also improves the joint movement as it provides a sensation of weightlessness. The hydrotherapy pool for the children must be provided with toys, balls pelvic jackets, gloves, flippers, balancing boards and other playful materials. This treatment improves the posture and other deformities in children as young as 6 months.[11] The treatment program which includes many exercises is very specific for each individual. Heated water in the pool provides relief from the joint pain and muscular relaxation. However, hydrotherapy is strongly discouraged when there is any kind of infection including skin, gastrointestinal, urinary tract and auditory canal infections. When the patient is immersed, metabolism is profoundly enhanced, more blood is supplied to the peripheral tissues due to vasodilation, heart rate and respiration rate increases. The heart rate and respiration rate returns to normal level once patient leaves the pool. After immersion, when the patient leaves the pool, the HR, RR, metabolic rate, and blood distribution normalize. The relaxation of muscle spasms and improvement of joint movement are the major therapeutic effects of hydrotherapy.[12]

Physiotherapy

Patients suffering from MPS have significant bone damage and require constant physiotherapy aiming to maintain their joint movement, thus helping them perform their daily activities. The most common problems associated with the disease include short stature, movement problems, joint alterations, vertebral column deformities, short neck, shortening of long bones, loss of grip and thorax bulging. Myofascial mobilization technique must be used to relax the muscles as it allows slow movement of the joints so as not to cause intense pain while improving the joint maneuvers.[13] The major aim of the respiratory physiotherapy is to improve the respiratory problems and improve the pulmonary exchange of gases. The respiratory problems arise due the muscle shortening, blockage in the upper airways, thorax protrusion, thus leading to the reduction in abdominal expansibility and sleep apnea. In such cases, physiotherapy literature recommends the use of postural drainage, expiratory flow acceleration maneuver for the drainage of fluid, cleansing of airways using saline solution and nebulization. To improve the pulmonary ventilation, the inspiratory and expiratory muscles should be properly stretched, relaxed, massaged and positioned. It is extremely important to properly guide the family members as respiratory physiotherapy must be carried out on daily basis.

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT), using cells from umbilical cord or bone marrow, can be used as a possible therapeutic method to prevent or even to reverse the major clinical features exhibited by MPS I. However, it carries with it a great danger of morbidity and death and this treatment must be performed before

the onset of major developmental disorders. The patient should be extensively assessed before undertaking HSCT procedure and must be regularly monitored..[14] In 1980, the first successful procedure for MPS I was carried out on 1 year old boy. Twelve months after the initial treatment, his L-iduronidase activity was enhanced, and a complete reversal of corneal clouding and hepatosplenomegaly was observed. After 20 years, the blood stem cells had begun producing normal blood cells, which meant that full engraftment was achieved. In addition, the patient was self-reliant, could operate computer and demonstrated medium range intelligence. Primarily, bone marrow cells are used for transplantation but there is a growing trend of using umbilical cord blood. To achieve successful engraftment, the pretransplantation preparation used for patient must be sufficiently immunosuppressive.[15]

Recent years have seen an increased survival rate for HSCT but still, the mortality rate is around 15%. The success of transplantation procedure depends upon the age of child, the efficiency of his cardiac and respiratory systems, the degree of compatibility between the donor and the patient's response to engraftment. The best therapeutic outcomes have been obtained in patients with the transplantation age of 2 years and developmental quotients of ~70. The most prominent outcome of HSCT is the reversal of intellectual disability in children, who otherwise, would have developed severe mental retardation. In addition, there is an improvement in joint movement, cardiopulmonary status and hearing contributing to the overall improvement in the individual's intellectual status. The clinical features of MPS I such as sleep apnea, upper airways obstruction may improve within the several months of initial transplantation. Moreover, glycosaminoglycans in the urine may return to normal level, the coarse facial features may improve and growth accelerates. The corneal clouding gets reversed and myocardial muscle function improves within the few years. However, skeletal system of the patient does not respond to HSCT and the improvement in this requires constant orthopedic care (Muenzer *et al*., 2009).

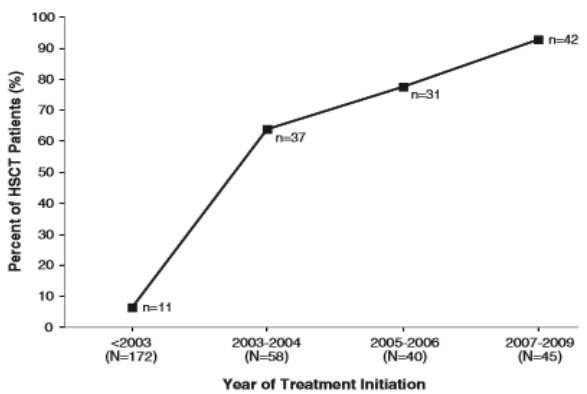

Figure 2: Number of MPS I patients treated with HSCT increased over the recent years.

Enzyme Replacement Therapy

In many countries, iduronidase enzyme have been approved for the treatment of MPS I. Many clinical trials have shown that the enzyme showed normal activity and was able to remove accumulated glycosaminoglycan. Iduronidase was intravenously injected into the MPS I patients with a dose of ~0.6 mg/kg of the body weight. Spleen and liver volume was reduced and there was a profound reduction in urinary glycosaminoglycan levels. Some patients demonstrated improved joint motion, clearing of vision and higher sleep apnea index.[16] As long as the enzyme was being administrated into the patients, these improvements sustained. Patients gradually became self-reliable as indicated by the improved ability to run, play sports and improved joint flexion. A placebo controlled, 26 week study was carried out on 45 MPS I patients and there was ~54% reduction in the urinary glycosaminoglycan levels. After 26 weeks of treatment, there was a 5.6% increase in the forced expiratory volume (FEV) and an improvement in the walk-test as compared to the patients who did not receive the actual enzyme.[17]

Due to the heterogeneous population of patients, the manifestations such as sleep apnea index and shoulder flexion did not significantly improve but an overall positive trend was obtained for the patients with severe disease. Although, IgG antibodies were produced against iduronidase by most of the patients, the clinical features (rashes, headache, fever) were generally managed by slowing the rate of enzyme infusion or administration of antihistamines. Only one of the patients experienced anaphylaxis which may have been triggered by the preexisting respiratory obstruction. The extent of a reaction depends upon the severity of respiratory problems associated with MPS I and may cause problems in managing the disease. A 6-year follow up study was carried out on 5 of the original patients and found that the amount of glycosaminoglycan in urine and liver size were stabilized, in contrast to the natural tendency of the disease. Patients were able to perform the daily activities of daily life. In those patients, the problem of left ventricular hypertrophy resolved but the aortic valves remained thick walled, even after 7 years of Iduronidase treatment. In the extension trial of phase 3, the effects of iduronidase enzyme on eyes were evaluated and it was found that visual acuity remained stable in at least 5 of the 8 participants. Iduronidase enzyme cannot cross the blood brain barrier and therefore, it is highly unlikely that it will improve the cognitive manifestations found in MPS I patients.[18]

Use of ERT With HSCT

It is safe to administer iduronidase along with HSCT and this may improve the engraftment rates by decreasing the clinical complications. However, the benefits obtained from the iduronidase administration after engraftment is a subject of intense debate. The patients with partial engraftment may get benefit from this procedure.[19]

Choice of the treatment method

MPS I disease is rare and shows multisystemic problems and thus, the involvement of specialized professionals from multiple disciplines is recommended to manage the disease. A team of professionals must be involved in determining the type of treatment a patient should get. This team must be at least three-membered consisting of a physician, a neurologist and a trained bone marrow physician. Depending upon the condition of the patient and severity of the disease, this team must design the optimal therapeutic strategy for the patient. The genotype of the MPS I patients should be determined as this may be helpful in deciding the optimum strategy. The understanding of genotype-phenotype correlations in MPS I are still limited but unpublished data and ongoing research shows that in the near future, we would be able to predict the genotype of a patient for a particular manifestation of the disease. This data will eventually be used for the screening of the newborn with MPS I disease.[20]

The patients with an age of <2.5 years and with the clinical signs of MPS I should receive HSCT. ERT will not be able to prevent the cognitive decline in patients as the enzyme is not able to cross the blood brain barrier. However, early HSCT may prevent the cognitive deterioration and prevent several manifestations of the disease. Therefore, HSCT is a preferred choice of treatment. MPS I patients with advanced nervous system disorders are highly unlikely to benefit from HSCT. 7. All MPS I patients (independent of whether they have received a graft or not) can get benefit from enzyme replacement therapy as this will reverse or preserve some somatic manifestations of the disease. Long-term ERT treatment may improve the quality of life for the patients. The ERT should be started at the early age as the efficiency of the treatment depends on this. Early initiation of the treatment will likely prevent the irreversible damage as indicated by a case study on two siblings with initiation of treatment at different ages.[21] There is no negative effect of ERT on engraftment. However, it must be kept in mind that the transplantation procedure should not be delayed for ERT.

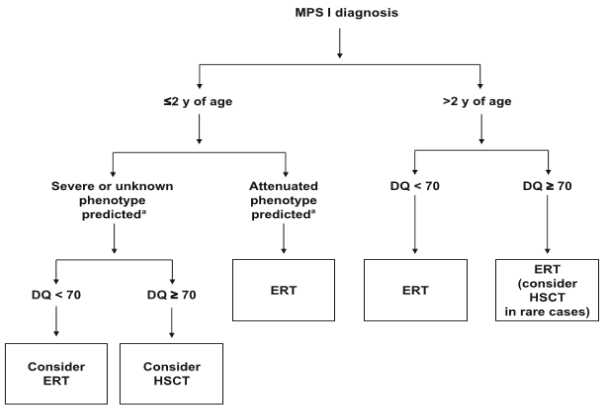

Figure 3: Choice of treatment method for MPS I patients.

Analysis of the treatment trends

Patient demographics

The demographics of the MPS I patients has been shown in the table 3. It indicates that at least half of the patients in the sample volume have Hurler syndrome. On the other hand, the patients showing the symptoms of hurler-scheie and Scheie syndromes comprise only a fraction of sample volume. More than 80% of the Caucasian patients were showing hurler syndrome (table 3). Some patients (~9%) of the patients were showing unknown symptoms. MPS I affected both males and females equally, thus showing the characteristic sign of an autosomal recessive disease. Consistent with the severity of clinical manifestations, the age of initial treatment was earliest for Hurler syndrome (maximally up to ~1.4 years), intermediate for hurler-scheie group (max. up to ~8.5 years) and latest for scheie syndrome (up to ~17 years). The median age at the onset of symptoms and diagnosis showed a similar trend as described above for each syndrome.[22]

Table 3: Demographic distribution of MPS I patients.

Region	Country	Number of patients
Europe and Middle East (47%, *n*=415)	Belgium	9
	Czech Republic	11
	Denmark	5
	France	63
	Germany	28
	Hungary	2
	Ireland	9
	Italy	26
	Netherlands	37
	Norway	1
	Poland	20
	Portugal	5
	Russia	1
	Saudi Arabia	2
	Slovakia	1
	Spain	25
	Sweden	4
	Turkey	3
	UK	163
North America (35%, *n*=313)	Canada	54
	USA	259
Latin America (15%, *n*=133)	Argentina	17
	Brazil	82
	Chile	7
	Colombia	6
	Mexico	20
	Venezuela	1
Asia Pacific (3%, *n*=30)	Australia	1
	Japan	8
	Korea	13
	New Zealand	1
	Singapore	1
	Taiwan	6
		Total 891

Chronology of symptom onset, MPS I diagnosis and treatment initiation

Figure 4 correlates the years less than 2003, 2003-05 and 2006-09 with the median age at the onset, diagnosis and treatment for each of the syndrome. It was observed that the median age at the onset of symptoms remained stable for the Hurler and Scheie patients whereas, it was reduced by a significant factor for the Hurler-scheie group after the year 2003. The median age at the diagnosis remained stable for all groups except for scheie syndrome where it increased in the years 2006-09. For all groups, the median age at the time of treatment decreased. A more significant decrease was observed for the scheie and hurler-scheie group as compared to the Hurler patients. The median interval between the diagnosis of disease and treatment for the Scheie patients is 1.4 years and for Hurler-Scheie group is 0.5 years during the years 2006-09. However, even after the approval of enzyme replacement therapy, this median interval remained unchanged.

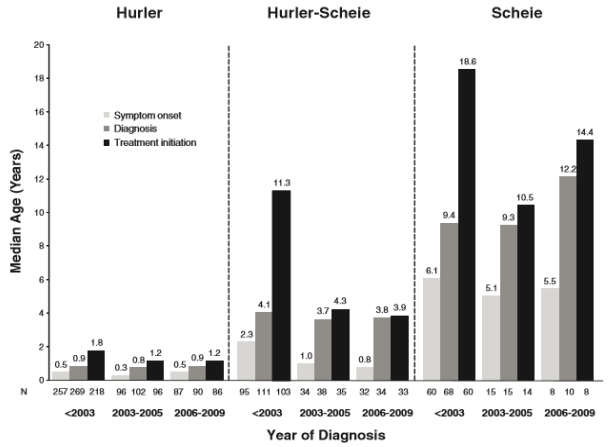

Figure 4: Symptom onset, diagnosis and treatment initiation for three groups of the patients.

HSCT and laronidase treatment trends

Although the median age at the time of HSCT has remained stable over the years, but the patients receiving stem cells from umbilical cord instead of bone marrow has increased sequentially over the years (26/158, 33/65 and 39/64 patients) (Figure 5). The majority of the stem cell donors were unrelated and the patients also received iduronidase administration. Nearly all of the patients who received ERT along with HSCT received it after the year 2003 (Figure 6).

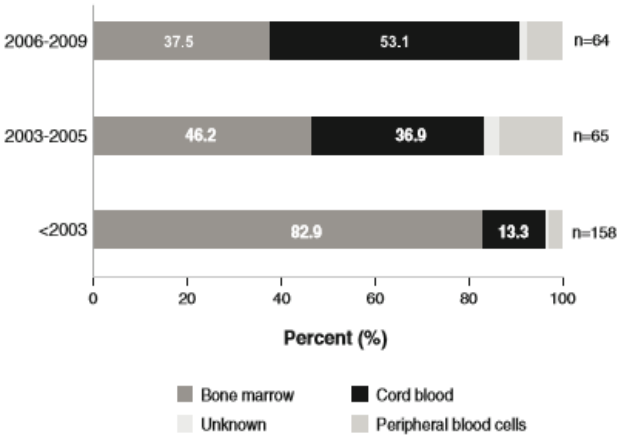

Figure 5: Choice of the stem cell sources for the patients treated with HSCT.

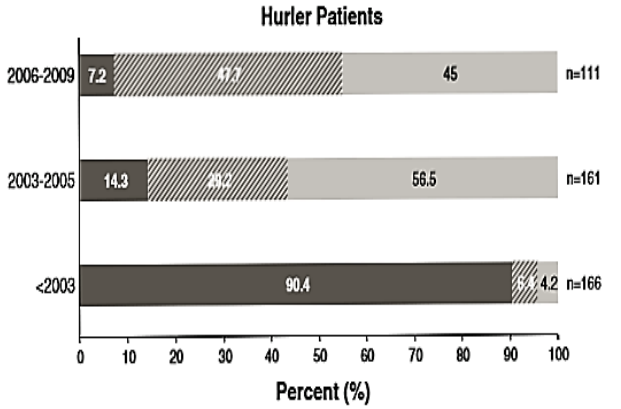

Figure 6: Choice of treatment trend for HSCT and ERT

KEY: BLACK= HSCT. LINED= HSCT + ERT. WHITE = ERT.

CONCLUSION

By proper identification and management of this disease, there is a better future for MPS I patients. Through the use of newborn screening, earlier detection of patients will be possible. Gene therapy may be used as a final assault to eradicate the disease. The main treatment currently available is the enzyme replacement therapy along with HSCT. Scientific advancement has provided valuable insights into the mechanism of MPS I and thus has helped in better management of the disease. Earlier detection of this disease and its proper treatment is the prime goal of the medical community today. Any experience gained with the MPS I must be shared with the world community with the aim of providing valuable assistance to the patients.

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