Original Article

Journal of Inborn Errors of Metabolism & Screening
2018, Volume 6: 1–12

DOI: 10.1177/2326409818759370
journals.sagepub.com/home/iem
SAGE

Outcomes of a Physician Survey on the Type, Progression, Assessment, and Treatment of Neurological Disease in Mucopolysaccharidoses

Maurizio Scarpa, MD, PhD[1], Paul R. Harmatz, MD[2], Bianca Meesen, MSc[3], and Roberto Giugliani, MD, PhD[4]

Abstract

The mucopolysaccharidosis (MPS) disorders are a group of rare, inherited lysosomal storage disorders. In each of the 11 MPS (sub)types, deficiency in a specific lysosomal enzyme (1 of 11 identified enzymes) leads to accumulation of glycosaminoglycans, resulting in cell, tissue, and multi-organ dysfunction. There is great heterogeneity in the clinical manifestations both between and within each MPS type. Somatic signs and symptoms include short stature, coarse facial features, skeletal and joint abnormalities, cardiorespiratory dysfunction, hepatosplenomegaly, and vision and hearing problems. In addition, patients with MPS I, II, III, and VII can have significant neurological manifestations, including impaired cognitive, language, and speech abilities, behavioral abnormalities, sleep problems, and/or epileptic seizures. Hydrocephalus is a frequent finding in patients with MPS I, II, and VI. Spinal cord compression can develop in almost all MPS disorders. Effective management and development of therapies that target these neurological manifestations warrant a profound understanding of their pathophysiology and progression in the different MPS types and best practices for evaluation and treatment. In order to obtain expert opinion addressing these topics we performed an online survey among an international group of experts with extensive experience in managing and treating MPS disorders. The results of this survey provide important insights into the management of neurological manifestations of MPS in clinical practice and are a valuable addition to current evidence.

Keywords

mucopolysaccharidoses, neurobehavioral manifestations, cognition disorders, survey, assessment, treatment

Introduction

The mucopolysaccharidosis (MPS) disorders are a group of rare lysosomal storage disorders which are inherited in an autosomal recessive manner, with the exception of MPS II (Hunter syndrome), which is X-linked. In each MPS, deficiency in a specific lysosomal enzyme causes progressive accumulation of glycosaminoglycans (GAGs), resulting in cell, tissue, and multi-organ dysfunction.[1,2] Somatic signs and symptoms of the 11 MPS types/subtypes (involving 11 specific enzymes) include short stature, coarse facial features, skeletal and joint abnormalities, cardiorespiratory dysfunction, hepatomegaly, and vision and hearing problems. The type and frequency of these symptoms vary considerably between and within the MPS types.

[1] Department of Paediatric and Adolescent Medicine, Helios Dr Horst Schmidt Kliniken, Center for Rare Diseases, Wiesbaden, Germany
[2] Department of Gastroenterology, UCSF Benioff Children's Hospital Oakland, Oakland, CA, USA
[3] Ismar Healthcare, Lier, Belgium
[4] Department of Genetics, UFRGS & INAGEMP and Medical Genetics Service, HCPA, Porto Alegre, Brazil

Received October 03, 2017, and in revised form December 01, 2017. Accepted for publication January 04, 2018.

Corresponding Author:
Maurizio Scarpa, MD, PhD, Department of Paediatric and Adolescent Medicine, Helios Dr Horst Schmidt Kliniken, Center for Rare Diseases, Ludwig-Erhard-Strasse 100, 65199 Wiesbaden, Germany.
Email: maurizio.scarpa@helios-kliniken.de

Neurological signs and symptoms, such as delay or decline/loss in milestone development (eg, language, speech, and cognitive ability), behavioral problems (eg, aggressive and/or hyperactive behavior), sleeping problems, and/or epileptic seizures, occur in patients with MPS I (particularly in the Hurler subtype [IH][3]), II (the neuropathic/severe form), III (Sanfilippo syndrome), and VII (Sly syndrome).[1,4-6] Most patients with MPS IV (Morquio syndrome) and VI (Maroteaux-Lamy syndrome) have normal cognitive development, although some studies and case reports showed brain abnormalities and/or cognitive problems in at least some of these patients.[7-10] Hydrocephalus is a frequent finding in patients with MPS I, II, and VI.[11] In addition, while spinal cord compression (SCC) can develop in all MPS disorders except MPS III and IX, patients with MPS I, II, and VI can present with carpal tunnel syndrome.[12]

In order to increase the understanding of the progression/natural history of neurologic disease in MPS, including optimal assessment and management, the authors organized an expert meeting on April 28 to 30, 2016, in Stockholm, Sweden, entitled "The Brain in MPS: Today and Tomorrow." This meeting was attended by an international group of 39 experts with experience in managing and treating MPS and/or basic scientists with expertise in pathophysiology, assessment, or treatment of central nervous system (CNS) disease. To prepare for the presentations and discussions at this meeting, the attendees were asked to complete an online survey prior to the meeting, evaluating their experience with and opinion on the management of neurologic disease in MPS. The results of this survey are discussed here.

Methods

The questionnaire for the online survey was developed by the authors in February and March 2016. A total of 37 experts/basic scientists attending the closed meeting received an e-mail invitation from the authors (the organizing committee of the meeting) to complete the survey in April 2016. Basic researchers attending the meeting who did not manage patients with MPS were not surveyed. The questionnaire (Appendix) included questions about respondent characteristics and experience with the different MPS disorders, types of neurological symptoms managed including established patient care goals, and how these neurological symptoms are assessed/monitored (with which tests) and managed/treated in the different MPS types. The preselected treatment options were bone marrow transplantation (BMT)/hematopoietic stem cell transplantation (HSCT); enzyme replacement therapy (ERT) administered via intravenous (IV), intrathecal (IT), or an alternate route (eg, intraventricular); surgery; other therapies (crossing the blood–brain barrier [BBB], not further specified); holistic/alternative therapy; and "I do not treat this MPS type." Responses were anonymous. As most patients with MPS IV and MPS VI have normal cognitive development, the questions focused on MPS I, II, III (A-D), VII, and IX. However, respondents were able to answer the questions for other MPS types as well, if felt appropriate.

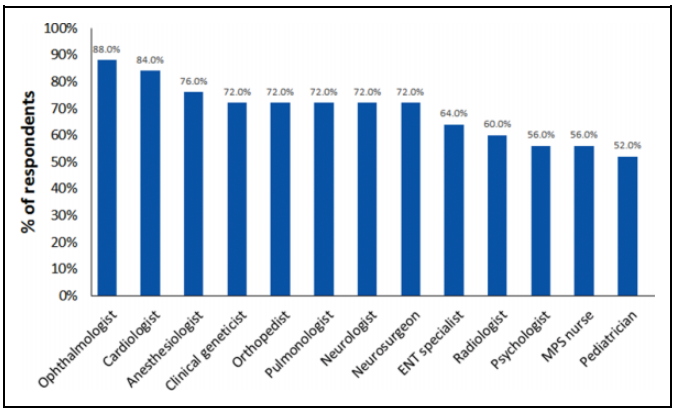

Figure 1. Specialists involved in the multidisciplinary patient care team (ticked by >50% of 25 respondents answering this question). ENT indicates ear, nose, and throat.

Results

Two of the 37 experts who received the e-mail invitation did not participate because they were not involved in patient care (see Acknowledgments for list of experts). The survey was completed by 27 (77%) of the 35 remaining experts; 24 (69%) respondents completed the entire survey. Combined results from the respondents who completely or partially completed the survey are presented; when responses were less than 27, this was because some respondents did not answer all questions.

Respondent Characteristics

Among the 35 respondents who participated in the survey, 12 (34%) were practicing in Europe, 11 (31%) in North America, 9 (26%) in Latin America, 2 (6%) in Asia, and 1 (3%) in Australia. About one quarter of respondents were pediatricians, almost one quarter were metabolic specialists or clinical geneticists, and another quarter (pediatric) neurologists. Most pediatricians and clinical geneticists had metabolism as a subspecialty. More than half of the respondents were the main clinicians coordinating patient management or the multidisciplinary team (n = 12 or 44%) and/or were involved in the diagnosis and management of MPS (n = 3 or 11%). Four experts were assessing or controlling neurodevelopmental (including speech), behavioral, or seizure problems; 2 experts did research in or performed and analyzed neuroimaging scans in patients with MPS. Most other respondents were taking care of patients on the ward or were involved in (outpatient) follow-up and treatment (including ERT). The majority of respondents (n = 25 or 93%) worked in a multidisciplinary team (Figure 1). In the past, most respondents had managed between 1 and 50 patients with MPS types associated with brain involvement, mainly MPS IH (N = 526), MPS II (N = 404), and IIIA-D (N = 343; Figure 2A). As expected, given the ultrarare nature of these MPS types, the respondents had limited or no experience taking care of patients with MPS VII or IX. Currently, most respondents were managing $\leq$10 patients per MPS

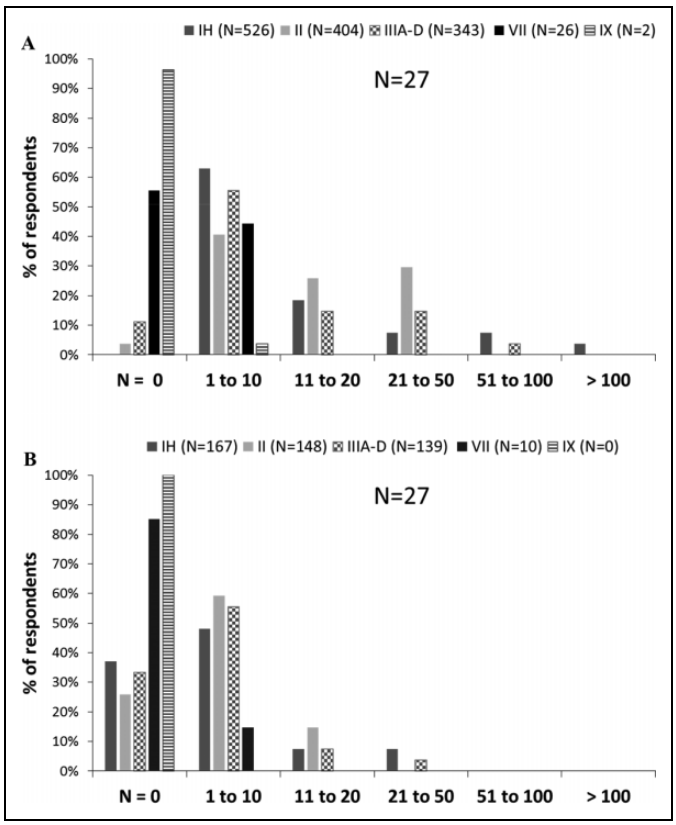

Figure 2. Percentage of respondents (A) ever or (B) currently managing patients with MPS IH, II, III(A-D), VII, or IX. IH indicates MPS I Hurler; MPS, mucopolysaccharidosis.

type (Figure 2B). Next to the preselected options MPS IH, II, IIIA-D, VII, and IX, some of the respondents added information on other MPS types. These respondents had collectively managed up to 25 patients with MPS I Hurler-Scheie (IHS), 149 patients with MPS IV (A-B), and 130 patients with MPS VI.

The CNS Symptoms and Care Goals

Neurodegeneration resulting in cognitive decline/impairment or dementia was considered the main brain/CNS problem, particularly in MPS III and the severe/neuropathic form of MPS II. Behavioral issues, loss of skills/communication, and epileptic seizures were also identified as important CNS problems. Developmental delay and cognitive decline causing loss of speech and attention, lack of communication, dependence on parents/caregivers for activities of daily living, hyperactive and aggressive behavior, and sleep disturbances were considered most troublesome for the family. Hydrocephalus and SCC were mentioned as major issues in MPS IH, MPS II, and MPS VI.

The main care goals were prevention (and management) of neurodegeneration, disease progression, and CNS manifestations. Improvement in mobility, communication, daily life/quality of life (QoL), and independence were also considered important. Main overall care goals shift with disease progression, from prevention of progression to management of

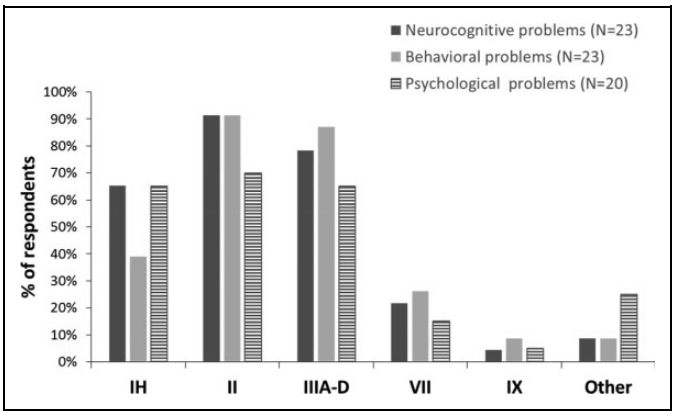

Figure 3. Percentage of respondents managing central nervous system (CNS) symptoms (behavioral, neurocognitive, and psychological problems) in MPS IH, II, IIIA-D, VII, and IX. IH indicates MPS I Hurler; MPS, mucopolysaccharidosis.

complications (behavior, seizures, hydrocephalus, SCC), with focus on family support, palliative care, and patient comfort/QoL. Most respondents recommended family support for cognitive, behavioral, and/or psychological symptoms.

Care goals differ between MPS types. In MPS III and severe/neuropathic MPS II, care focuses on cognitive impairment/dementia, behavioral alterations (eg, hyperactivity), and seizures. In MPS I(H), II, and VI, hydrocephalus and SCC are considered most important. It was put forward that, despite normal cognition, patients with MPS IV and VI can suffer from anxiety and depression. It is important to note that most patients with MPS IH currently undergo BMT/HSCT, resulting in a very modified, less severe neurologic progression than untransplanted MPS IH.

Multidisciplinary management consisting of regular multisystemic assessments, including neurological/cognitive examination, brain/spine imaging, electroencephalography (EEG), and polysomnography (PSG), was considered crucial. Based on the outcomes, patients can be referred to other specialists for management. Management involves treatment of disease manifestations and complications, planning and monitoring of treatment, identification of challenges in daily life, assistance at school, supportive training, and arrangement of other facilities.

Main CNS Symptoms Managed by MPS Type

Figures 3–5 and Table 1 show in which MPS types the respondents managed specific CNS symptoms. Neurocognitive, behavioral, feeding/swallowing, and sleep problems were mainly managed in MPS II and III and less frequently in MPS IH (probably mostly posttransplant). Seizures were predominantly managed in MPS III and less frequently in MPS II (Figure 5). Psychological problems, neuromuscular dysfunction (NMD; eg, myoclonus, spasticity, dystonia, ataxia, paralysis, change in coordination/balance, weakness, slurred speech, tremors), and nonspecific CNS symptoms (predominantly headaches and vision changes) were managed frequently in all 3 MPS types

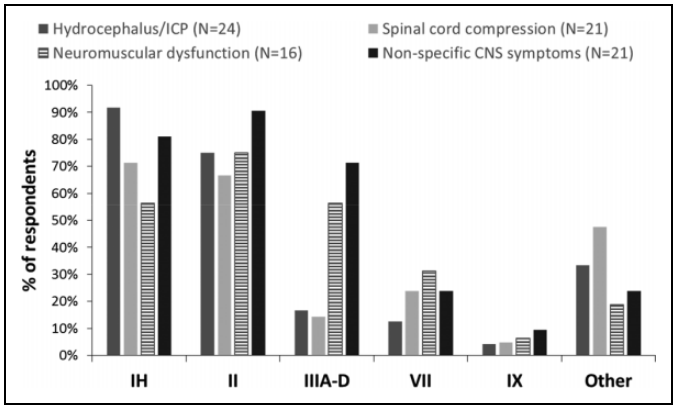

Figure 4. Percentage of respondents managing secondary central nervous system (CNS) symptoms in MPS IH, II, IIIA-D, VII, and IX. ICP indicates intracranial pressure; IH, MPS I Hurler; MPS, mucopolysaccharidosis.

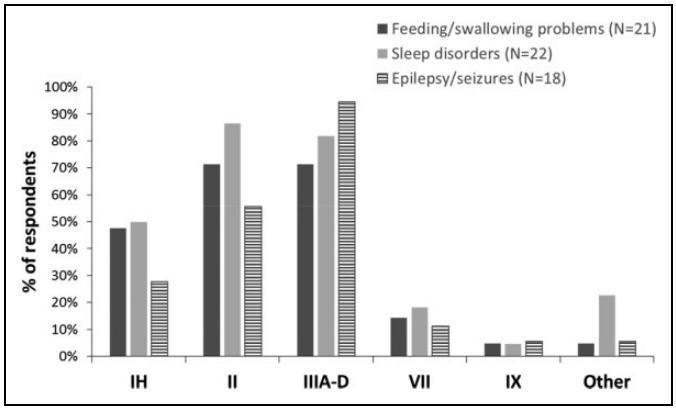

Figure 5. Percentage of respondents managing feeding/swallowing and sleep disorders and seizures/epilepsy in MPS IH, II, IIIA-D, VII, and IX. IH indicates MPS I Hurler; MPS, mucopolysaccharidosis.

(IH, II, and III). Around 25% of respondents also managed psychological symptoms (anxiety and depression) in MPS IHS, IV(A), and VI. Both NMD and sleep problems were also managed in MPS IV and MPS VI.

Increased intracranial pressure (ICP) or hydrocephalus and SCC were mainly seen and managed in patients with MPS IH and MPS II (Figure 4). Increased intracranial pressure/hydrocephalus was also managed in other MPS types, mainly MPS VI; SCC has also been managed in MPS VI and MPS IV.

Assessments Performed per MPS Type

Table 2 provides an overview of assessments ordered routinely for different MPS types. Over half of the group routinely ordered cervical spine imaging, brain magnetic resonance imaging (MRI), sleep studies, neurocognitive tools, psychological tools, EEG, and QoL tools.

Cervical spine imaging and brain MRI were most often ordered for patients with MPS IH and II and less frequently for MPS III (Table 2), for monitoring hydrocephalus and SCC (Table 3). One-third of respondents reported that they also used

Table 1. Major Brain/CNS Problems by MPS Type.[a]

MPS Type	Major Neurological Manifestations
III and (severe/neuropathic) II	More: • Cognitive impairment/dementia • Behavioral abnormalities/ hyperactivity • Seizures/epilepsy • Sleep problems
I (H)[b] (vs III and II)	Lower prevalence of: • Cognitive impairment • Sleep problems • Feeding/swallowing problems
I (H)[b] and II	Higher prevalence of hydrocephalus and SCC
I, II and VI	More secondary complications: • SCC (also in IV) • Hydrocephalus
VI	Silent optic nerve compression
IV and VI	Along with disease progression: • Anxiety • Depression
	Sleep problems (particularly in VI)

Abbreviations: CNS, central nervous system; MPS, mucopolysaccharidosis; SCC, spinal cord compression.
[a]N = 24.
[b]Most patients with MPS I Hurler (IH) mostly likely underwent early hematopoietic stem cell therapy (HSCT), in line with management guidelines.

these tests routinely in MPS IV(A) and VI. It should be noted that information on MPS IHS, IV, and VI was only entered if the respondent felt this was appropriate. Cervical spine imaging was generally ordered yearly and brain MRI yearly or as needed, with the frequency varying with disease progression and clinical symptoms.

Sleep studies were predominantly ordered routinely for patients with MPS IH, II, and III (Table 2), but also often for patients with MPS IV(A) and VI. The frequency often depended on disease progression.

An EEG was most commonly ordered for monitoring seizures or sleep problems in MPS II and III and less frequently for patients with MPS IH (Tables 2 and 3), mainly as needed and depending on disease progression.

Neurocognitive and psychological tools were particularly ordered for patients with MPS IH, II, and III (Table 2), but also often for MPS VII and VI. Psychological tools were also ordered for MPS IV. Neurocognitive function/developmental quotient (DQ) testing was mostly done yearly or as needed, often depending on disease progression. The Bayley Scales of Infant Development (BSID), Vineland Adaptive Behavior Scales (VABS), Differential Ability Scales (DAS), Wechsler Preschool and Primary Scales of Intelligence (WPPSI), Wechsler Intelligence Scale for Children (WISC), and/or Wechsler Adult Intelligence Scale (WAIS) were frequently used. The VABS, Strength and Difficulties Questionnaire, Child Behavior Checklist, and Social Communication Questionnaire were often used for psychological testing, mainly as needed, with the frequency often depending on disease progression.

Table 2. Responses to the Question "For Which MPS Types Did/Do You Order the Following Tests Routinely?"[a]

		% of Responses per MPS Type					
	Responses	IH (%)	II (%)	IIIA-D (%)	VII (%)	IX (%)	Other (%)
Brain MRI	21	95.2	95.2	71.4	33.3	9.5	38.1
Brain MRS	1	0	100	100	0	0	0
Brain fMRI	1	0	100	100	0	0	0
Brain CT	7	85.7	85.7	57.1	14.3	0	42.9[b]
EEG	13	76.9	92.3	92.3	15.4	7.7	15.4
BAER	11	100	100	100	45.5	0	36.4
Cervical spine imaging	22	100	100	40.9	36.4	9.1	36.4
ICP	10	100	80.0	20.0	20.0	0	50.0
VEP	7	85.7	100	71.4	28.6	14.3	57.1[c]
VERG	7	71.4	100	71.4	14.3	14.3	42.9[c]
Sleep study	19	100	100	73.7	36.8	5.3	36.8
Neurocognitive tools	17	100	100	94.1	41.2	5.9	29.4
Psychological tools	14	92.9	100	100	42.9	14.3	28.6
QoL tools	13	92.3	92.3	76.9	38.5	23.1	46.2
Pain tools	9	88.9	100	66.7	44.4	44.4	44.4

Abbreviations: BAER, brain auditory evoked response; CT, computed tomography; EEG, electroencephalography; fMRI, functional MRI; ICP, intracranial pressure; MPS, mucopolysaccharidosis; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; QoL, quality of life; VEP, visual evoked potential; VERG, visual evoked retinography.
[a]Assessment ordered by at least 10 respondents overall and for a specific MPS type are marked.
[b]MPS IV and VI.
[c]Mainly MPS VI.

QoL tools were primarily ordered for patients with MPS IH and II and less frequently for MPS III (Table 2), but by around half of the respondents also for patients with MPS IV and VI. The QoL questionnaires used, mainly as needed, were the MPS Health Assessment Questionnaire, the Short-Form 36, and Pediatric Outcomes Data Collection Instrument. Pain assessment tools were used by a limited number of respondents, as needed, and included a visual analog scale or the modified Wong pain faces. Only 10 respondents ordered ICP measurement (mainly as needed, depending on disease progression), predominantly for patients with MPS IH, II (Table 2), and VI.

Monitoring and Management of CNS Symptoms

Table 3 shows which CNS symptoms were seen, how and with which frequency they were monitored, and how they were managed. Assessments for behavioral and psychological symptoms, feeding/swallowing problems, and epileptic seizures were ordered as needed. Sleep disorders were mostly monitored yearly. There was less agreement among the respondents about the frequency for monitoring other neurological manifestations, that is, neurocognitive function, increased ICP or hydrocephalus, SCC, neuromuscular disorders, and nonspecific CNS symptoms such as headache, vision changes, pain crises, autistic traits, or tremors.

Management of neurocognitive, behavioral, and psychological symptoms was palliative (behavioral, educational, relaxation, and psychological therapy), with support of a psychologist. CNS medications such as antipsychotics and neuroleptics were also prescribed to treat behavioral symptoms. Anticonvulsants were prescribed to manage epileptic seizures. In addition, anxiolytics, antidepressants, and antipsychotics were sometimes prescribed for psychological (anxiety and depression) symptoms. These medications were particularly used when symptoms progressed and with caution for overmedication. Respondents indicated that medication for psychological symptoms is effective only for a short time. Medication was also used to treat spasticity and nonspecific CNS symptoms such as headache, tremors/myoclonus, and pain. Physiotherapy was applied for treating impaired fine motor skills and balance, muscle weakness, gait disturbance, secretions, and aspiration pneumonias. Both ICP/hydrocephalus and SCC were treated with surgery, that is, shunting and decompression surgery. Feeding/swallowing symptoms were initially managed with food modification and swallowing training. If not successful, nasogastric tube feeding was recommended, particularly in case of recurrent aspiration pneumonias. Gastrostomy tube feeding was used as a last resort. Recurrent epileptic seizures were managed with antiepileptic drugs (AEDs). Sleep disorders were managed with ear, nose, and throat surgery (in case of enlarged adenoids and/or tonsils), ventilation support systems, behavior modification, or medications such as melatonin, antihistamines, and tryptophan, depending on the underlying cause.

Treatment Options for Replacing the Deficient Enzyme

Most respondents selected HSCT/BMT as the most impactful treatment option for patients with MPS IH (Figure 6), mainly to halt or delay neurocognitive decline, although they indicated it may also stabilize other manifestations such as skeletal,

Table 3. Assessment and Management of Specific CNS Symptom(s).

CNS Symptom(s)	Assessment/Monitoring		Management
	By:	When: n (%)	
Neurocognitive: • Neurocognitive decline • Progressive development delay • Decrease in DQ, attention, short-term memory, and learning ability • ADHD • Delay in speech/language • Delay in fine and gross motor function • Dementia	• Clinical examination • Neurological examination[a] • Parents/caregiver and school reports	• Monthly: 1 (4.8%) • Yearly: 8 (42.9%) • As needed: 11 (52.4%)	• Psychoeducational therapy • Cognitive behavioral therapy • Speech/swallowing therapy • Relaxation therapy • Occupational therapy • Physiotherapy (for fine motor skills balance) • Walking aids • ADHD medication[b] • Central stimulation medication • Referral for IT ERT • Discussions with school concerning need for more time and a special class (environment)
Behavioral: • Hyperactivity • Aggressive, impulsive disruptive behavior • Emotional outbursts/ temper tantrums • Lack of fear, with dangerous behaviors exhibited by patient toward themselves and family • Autistic features	• Clinical observation • Psychological examination • Questionnaires for patients and parents/caregiver • Interviews with parents/caregiver and teachers	• Monthly: 2 (10.0%) • Yearly: 6 (30.0%) • As needed: 12 (60.0%)	• Parental education • Referral for psychological/behavioral support • Medication: antipsychotics, neuroleptics, and anticonvulsants[c]
Psychological: • Anxiety • Depression • Emotional instability • Psychosis • Hyperactivity • ADHD • Aggression • Autistic behavior	• Clinical observation • Psychological examination • Questionnaires for parents • Interviews with parents/caregiver	• Monthly: 1 (5.9%) • Yearly: 4 (23.5%) • As needed: 12 (70.6%)	• Referral to psychologist • Psychotherapy (for behavior modification) • Medication: anxiolytics, antidepressants, and antipsychotics[d] • Avoiding an overload of noise and other irritations or stimulants • Snoezelen room[e] • Music therapy

Increased ICP/hydrocephalus	• Clinical findings (eg, headache)
	• Neurological examination
	• Brain CT and MRI (Evan's index and width 3rd ventricle)
	• Lumbar puncture with (opening) CSF ICP measurement
	• Head circumference (increases especially when sutures still open)
	• Eye fundoscopy (papilledema is a sign of increased ICP)[f]
		• Yearly: 12 (54.6%)
		• As needed: 9 (40.9%)
		• Not known: 1 (4.6%)
			• VP (programmable) shunt
			• Referral to neurosurgeon for advice (on shunt placement)
			• A shunt is placed
			  ○ at confirmation of increased ICP (>20-25 cm H_2O) during lumbar puncture, with ventricular dilatation/ severe hydrocephalus (in the presence of symptoms such as reflexes and seizures or symptoms deterioration)
			  ○ at recommendation by the neurosurgeon

(continued)

Table 3. (continued)

CNS Symptom(s)	Assessment/Monitoring		Management
	By:	When: n (%)	
SCC	• Clinical signs and symptoms (numbness, walking problems, tingling) • Physical and neurological examination ([median nerve] SSEP, EMG) • Spine MRI (sometimes tridimensional CT)	• Monthly: 2 (10.5%) • Yearly: 8 (42.1%) • As needed: 8 (42.1%) • Not known: 1 (5.3%)	• Spinal (decompression) surgery to avoid myelopathy ○ At clinical deterioration (muscle weakness resulting in gait problems, falls, tiredness, and/or focal neurological signs) with ○ EMG/SSEP abnormalities and ○ Compression and cord injury visible at MRI • Monitoring SCI by regular clinical and MRI follow-up • Avoiding SCI by recommending patient/parents to avoid overweight, contact sports, other potentially dangerous activities, or specific neck movements (neck brace for fixation)
NMD: • Muscle weakness • Gait/balance/coordination disturbance • Toe walking • Myoclonus • Spasticity • Ataxia • Dysphagia	• Clinical examination • Physical examination, including ENT • Neurological examination: EMG • MRI • 6MWT	• Monthly: 1 (7.7%) • Yearly: 6 (46.2%) • As needed: 6 (46.2%)	• Depends on abnormality • SCC: fusion and laminectomy • Physiotherapy • Supportive aids[g] • Gastrostomy • Spasticity medication: baclofen, botulinum toxin, or clonazepam
Nonspecific CNS symptoms • Headache: MPS I • Vision (hearing) changes • Sleep disorders: MPS II and III • Mutism and pain crisis: MPS II • Autistic traits: MPS III • Tremors and myoclonus: MPS III	• Clinical examination • Physical examination • Neurological examination • Ophthalmological examination • Audiological examination • Parents reports	• Monthly: 1 (6.7%) • Yearly: 7 (46.7%) • As needed: 7 (46.7%)	• Symptomatic • Headache: paracetamol • Tremors/myoclonus: clonazepam (very low dose) • Pain crises: pain medication • Referral to ophthalmologist; magnifying glasses • Hearing aids
Feeding/swallowing problems	• Clinical examination, including weight (control) • ENT • Neurological examination • Pneumological examination • GE examination[h] • Endoscopy • Imaging (X-ray) • Patient's report • Parents/caregiver reports	• Yearly: 6 (33.3%) • As needed: 12 (66.7%)	• Food modification: alteration of food thickness or high-calorie diet • Swallowing training • Nasogastric tube feeding[i] • Surgery: gastrostomy for tube feeding (as last resort) ○ Secretions: kinesiotherapy, suction, aspiration, medication (inhaled corticosteroids, bronchodilators, antibiotics, atropine eye drops, scopolamine, botulinum toxin, ERT), CPAP ○ Aspiration pneumonias: food modification, (pulmonary) physiotherapy, (aggressive) antibiotic therapy, (nasogastric or gastrostomy) tube feeding
Sleep disorders	• Parents/caregiver history • Sleep studies (PSG/EEG/EMG) • RFT studies	• Monthly: 2 (11.1%) • Yearly: 10 (55.6%) • As needed: 6 (33.3%)	• Correction of sleep position • Behavior modification (eating and sleeping patterns) • Improvement of respiratory function • Medication: melatonin (high doses), antihistamines, tryptophan, ERT

(continued)

Table 3. (continued)

CNS Symptom(s)	Assessment/Monitoring By:	Assessment/Monitoring When: n (%)	Management
Seizures/epilepsy • Mostly: generalized tonic–clonic • Sometimes: partial (simple or complex)	• Clinical examination • Neurological examination • Caregiver history • (video) EEG • (CT/MRI)	• Monthly: 1 (6.3%) • Yearly: 4 (25.0%) • As needed: 11 (68.8%)	• Ventilation by CPAP/BiPAP (initiated by sleep specialist) • ENT surgery (adenoids and/or tonsils) • Diet • AEDs (in consultation with or prescribed by neurologist); first seizure usually not treated • Status epilepticus (with support from neuro/epilepsy team): ○ Anticonvulsants ○ Benzodiazepines (to be taken with care): midazolam, diazepam, or lorazepam, or IV levetiracetam or topiramate ○ Phenobarbital ○ Intubation and anesthetic drugs at the ICU (if not stopped)

Abbreviations: ADHD, attention-deficit hyperactivity disorder; ADL, activities of daily living; AED, antiepileptic drug; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CSF, cerebrospinal fluid; CT, computed tomography; DQ, developmental quotient; EEG, electroencephalography; EMG, electromyography; ENT, ear, nose, throat; ERT, enzyme replacement therapy; GE, gastroenterology; ICP, intracranial pressure; ICU, intensive care unit; IT, intrathecal; IV, intravenous; MRI, magnetic resonance imaging; 6MWT, 6-minute walk test; NMD, neuromuscular dysfunction; PSG, polysomnography; RFT, respiratory function test; SCC, spinal cord compression; SCI, spinal cord injury; SSEP, somatosensory evoked potential; VP, ventriculoperitoneal.

[a]For example, developmental (motor and intelligence), (age-appropriate) neurocognitive, and neuropsychological testing.

[b]Risperidone, atomoxetine; caveat: overmedication can cause adverse events.

[c]Overmedication, ADHD, and some antipsychotics should be avoided.

[d]Overmedication with antipsychotics as well as ADHD medication should be avoided, and anxiolytics can cause respiratory depression and some medications lower seizure threshold in MPS III.

[e]Therapy for people with autism and other developmental disabilities, dementia, or brain injury. Patient is placed in a soothing and stimulating environment, called the "Snoezelen" room (as the concept was developed in the Netherlands). These rooms are specially designed to deliver stimuli to various senses, using lighting effects, color, sounds, music, scents, and so on.

[f]According to a publication by Beck and Cole, papilledema in fundoscopy is an unreliable signal for increased ICP in patients with MPS.[13]

[g]For example, orthotics, corsets, wheelchair.

[h]Including a (modified barium) swallowing videofluoroscopy test.

[i]In case of recurrent aspiration pneumonias or when swallowing is so difficult that it results in weight loss. It is recommended not to wait too long to proceed with tube feeding; this may require counseling of the parents to persuade with tube feeding quickly.

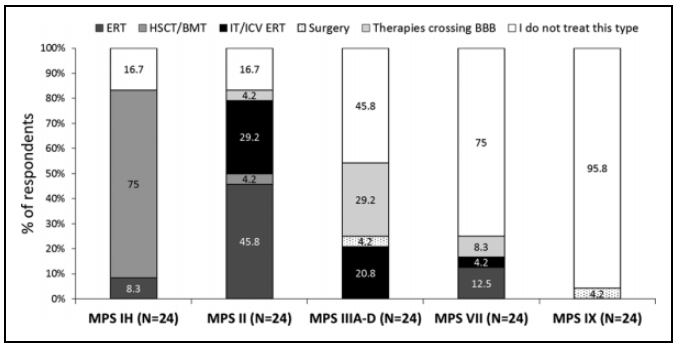

Figure 6. Treatment options considered to have the most impact. Percentage of respondents responding positive for ERT (IV or by IT/ICV or alternate route), HSCT/BMT, surgery, or other therapies crossing the BBB. Alternate ERT delivery and holistic were not used by any of the respondents. BBB indicates blood–brain barrier; BMT, bone marrow transplantation; ERT, enzyme replacement therapy; HSCT, hematopoietic stem cell therapy; ICV, intracerebroventricular; IT, intrathecal; MPS, mucopolysaccharidosis.

cardiorespiratory, and ophthalmological abnormalities. Most respondents believed that HSCT/BMT provides symptomatic care.

Enzyme replacement therapy (either IV, IT, or intracerebroventricular [ICV]) was considered most effective in patients with MPS II and MPS III (Figure 6) and in other MPS types such as MPS IHS, MPS IV(A), and VI. While IV ERT is an approved treatment option for MPS I, II, IVA, and VI, ICV or IT administration of ERT is currently still experimental and only available in a clinical trial setting (for MPS I, II, and IIIA and IIIB).[14-17] For patients with MPS II, both IV administration and IT/ICV administration were considered effective; for patients with MPS IIIA, only IT/ICV ERT was considered effective. The respondents used IV ERT to treat somatic manifestations (of the joints, lungs, and heart), slow down disease progression, and improve the patient's overall condition/QoL. The IT/ICV ERT was considered to reestablish normal enzyme function and reduce GAG storage in the brain and to stop neurocognitive decline and behavioral problems.

Other (experimental) therapies crossing the BBB, such as gene therapy, were considered mainly impactful in patients MPS III and, to a lesser extent, in patients with MPS VII and MPS II.

Almost half of the respondents had not treated patients with MPS III, although it is among the most frequent MPS disorders.[2] This may be due to the fact that no approved disease-specific therapy is currently available for MPS III and because patients with MPS III have less somatic issues than patients with other MPS disorders. They hardly treated any patients with MPS VII and MPS IX, which are very rare and have no approved treatments (Figure 6).

Discussion

Current literature regarding the clinical management of neurological manifestations of MPS is relatively limited. The present survey assessed how these manifestations are managed in clinical practice. The survey focused on MPS types with potential brain/CNS involvement, that is, IH, II, IIIA-D, VII, and IX. As the respondents had only limited experience in managing MPS VII and IX, due to their ultrarare nature, the survey outcomes for these types were not discussed in detail. In addition, as information on other MPS types such as MPS IHS, IV, and VI was only entered by the respondents if they felt this was appropriate, the outcomes for these MPS types should be considered incomplete. Another limitation is that web-based surveys may be biased by low, selective, and incomplete participation. Despite these limitations, the survey provided important insights into the evaluation and management of MPS-related CNS disease in clinical practice. Overall, the survey outcomes were largely in line with published management guidelines, although these were often not available.

In line with published findings, the survey results show that developmental delay, cognitive decline, behavioral problems, sleep disturbances, and seizures are most frequently present in MPS disorders associated with accumulation of heparan sulfate, that is, MPS III, MPS II (mainly the neuropathic form[18,19]), and MPS I (mainly IH).[20-26] Although the majority of patients with MPS IV and VI have preserved cognition, they can become anxious and depressed when the disease progresses, probably because they understand the severity of their disease. In patients with MPS IH, MPS II, and VI, associated with accumulation of dermatan sulfate, hydrocephalus and SCC were considered important CNS problems, which is also in line with published findings.[26,27] Not surprisingly, care goals differed along the same lines between the MPS types. Care goals were also dependent on disease stage, focusing on prevention of neurodegeneration and neurological progression in the early stages and on the management of complications, palliative care/patient comfort, and family support in the later stages.

Overall, the evaluation and management of CNS manifestations of MPS by the survey respondents were largely supported by the current literature, when available. Neurocognitive, developmental, and behavioral tests used frequently by neuropsychologists, that is, the BSID (Bayley's), DAS, VABS (Vineland's), and WPPSI/WISC/WAIS (Wechsler's), are also most commonly used in clinical trials or practice.[28] It should be noted that some of these tools take long to complete and are therefore not suitable for routine screening, suggesting respondents use them in the framework of clinical trials. However, the influence of participation in clinical trials on these answers could not be confirmed as involvement in clinical trials was not addressed in the survey. Surprisingly, neurocognitive/psychological tools are often ordered for patients with MPS VI and IV, although most of these patients are believed to have preserved cognition and it can be hard to get insurance authorization for neurocognitive studies in some countries. Nevertheless, some studies have shown that brain abnormalities and/or neurocognitive problems may occur in these patients.[7-10] Therefore, further study is warranted to assess whether these patients might benefit from neurocognitive/psychological evaluation. Management approaches for cognitive and behavioral symptoms included psychoeducational, behavioral, speech/swallowing, relaxation, and occupational therapies; physiotherapy for fine motor skills; pharmacological therapy with antipsychotics, neuroleptics, anxiolytics, and antidepressants; and attention-deficit hyperactive disorder medication. Current evidence for the efficacy of these therapies in patients with MPS is very limited and often shows variable outcomes.[29,30] The use of AEDs to reduce the frequency and/or duration of seizures is supported by several studies, although evidence for specific drugs is limited.[31]

Brain MRI/computed tomography (CT) and evaluation of ICP were most frequently performed in patients with MPS I and II, who are most likely to develop hydrocephalus.[11,32,33] At the time of the survey, there were no formal guidelines for the evaluation of hydrocephalus in patients with MPS. Respondents of the survey recommended regular monitoring for headaches, ventriculomegaly (with a CT and/or MRI scan), or increased ICP (by lumbar puncture).[34] Increases in ICP to >25 cm H_2O or development of hydrocephalus warrants referral to a neurosurgeon for advice on ventriculoperitoneal shunt placement.[34] Comparable recommendations have been made in a recent publication by Dalla Corte et al.[35] Spinal cord compression was most frequently managed in patients with MPS IH, II, IV, and VI, in accordance with the high risk of SCC in these patients.[36,37] Evaluation of SCC by clinical signs and symptoms, physical and neurological examination, and spine/brain MRI is largely in line with published recommendations.[34,36-38] Consulting patients and parents about the risks of overweight, contact sports and other dangerous activities, and/or the need for neck fixation was considered to reduce the risk of spinal cord injury (if surgery is delayed). Likewise, published expert recommendations warn for the risk of atlantoaxial subluxation and cervical myelopathy with sudden or vigorous hyperreflexion or hyperextension during neck manipulations or falls.[36-38] In the respondents' opinion, and in line with published findings, increased ICP/communicating hydrocephalus and SCC in patients with MPS requires surgical management.[36,37,39,40]

Sleep disturbances were reported for all MPS disorders, confirming published data.[41,42] Sleep studies were frequently used by the respondents of the survey. Regular respiratory function tests and questioning parents/caregivers about potential sleep disturbances were also mentioned. Sleep studies to detect sleep-disordered breathing have been recommended for all patients with MPS at diagnosis and based on the presence of symptoms such as snoring, daytime somnolence, or development of respiratory failure.[43] Although sleep-disordered breathing is not common in patients with MPS III, CNS-related sleep disturbances are almost universal in these patients and also frequently occur in patients with MPS II.[41] Both PSG with EEG may be useful to detect abnormal brain function during sleep in these patients.[41] Management of sleep-disordered breathing by the respondents with tonsillectomy/adenoidectomy and ventilation support systems is supported by the literature, as is the use of melatonin to manage non-respiratory sleep disturbances.[43,44] The use of antihistamines or tryptophan to treat sleep disorders in patients with MPS, as suggested by some respondents, is currently not supported by published data.

Epileptic seizures were mainly managed in patients with MPS III and MPS II, in line with published observations.[31,45] They were usually reported by parents or caregivers. According to the respondents, recurrent seizures confirmed on EEG can be treated by one or, if needed, more AEDs, in close cooperation with the neurologist. The limited published evidence currently available confirms that AEDs are generally effective in controlling seizures in patients with MPS, although information on the efficacy and safety of specific drugs in these patients is lacking.[31]

The respondents selected HSCT/BMT as the most impactful treatment for MPS IH. HSCT/BMT is the recommended treatment option for this MPS type,[3,27] as it can halt or delay neurocognitive decline if started early (<2 years) in patients with a DQ $\geq$70.[46] Enzyme replacement therapy was considered most effective for patients with MPS II, mainly for reducing somatic manifestations, improving related QoL, and slowing down disease progression. Although IV ERT can improve somatic symptoms of MPS II,[47] it has no impact on CNS manifestations due to the inability of the recombinant enzyme to cross the BBB. Somewhat surprisingly, several participants selected IT/ICV ERT as effective therapies for MPS II and III. These results are remarkable as these therapies have only been tested in small clinical trials and require confirmation of efficacy in further studies.[15,16] Possibly, these respondents have enrolled patients in clinical trials with these experimental therapies. In line with published (international) guidelines,[48,49] IV ERT was selected as the most impactful treatment for patients with MPS IV (A) and VI. In these patients, ERT can reduce somatic manifestations and slow down disease progression.[50,51]

Conclusion and Future Directions

The results of the present survey provide important insights into the management of neurological manifestations of MPS in clinical practice. They confirm that neurocognitive and behavioral signs and symptoms very frequently occur in MPS III and neuropathic MPS II and, to a lesser extent, in MPS IH post-HSCT, while patients with MPS IH, VI, and/or IV are more prone to develop neurological manifestations secondary to somatic disease, that is, hydrocephalus and SCC. The management of neurological manifestations in patients with MPS in clinical practice appears to be largely in line with the current literature. However, due to the rarity of the MPS disorders, objective published data are scarce and recommendations are often lacking or based on clinical experience only. This underscores the need for more objective clinical data on neurological manifestations of MPS and on the effects of treatment on these manifestations in the different MPS disorders. In the absence of clinical data, expert experience can be a valuable addition to current evidence.

Authors' Note

BioMarin participated in the creation of the survey, but interpretation of the data and writing of the manuscript were done by Ismar Healthcare, in cooperation with the authors (sponsored by BioMarin). Both the authors and BioMarin reviewed the manuscript and approved the final version before submission.

Acknowledgments

The authors are grateful to Ismar Healthcare NV for their assistance in the writing of this manuscript, which was funded by BioMarin Pharmaceutical Inc. The expert meeting in Stockholm was also sponsored by BioMarin Pharmaceutical Inc. The authors are also grateful to the experts who were invited to participate in the premeeting online survey: Tord D. Alden, Chicago, Illinois; Hernán Amartino, Buenos Aires, Argentina; Rita Barone, Catania, Italy; Lorne A. Clarke, Vancouver, British Columbia, Canada; Amauri Dalla Corte, Porto Alegre, Rio Grande do Sul, Brazil; Katleen A. Delaney, Mendota Heights, Minnesota; Patricia I. Dickson, Torrance, California; Carolyn Ellaway, Sydney, New South Wales, Australia; Maria L. Escolar, Pittsburgh, Pennsylvania; Wendy Heywood, London, United Kingdom; Rachel Honjo, São Paulo, Brazil; Dafne D. G. Horovitz, Rio de Janeiro, Brazil; Simon A. Jones, Manchester, United Kingdom; Christina Lampe, Wiesbaden, Germany; Florian Lagler, Salzburg, Vienna, Austria; Charles Marques Lourenço, São Paulo, Brazil; John J. Mitchell, Montreal, Québec, Canada; Joseph Muenzer, Chapel Hill, North Carolina; Nicole Muschol, Hamburg, Germany; Karin Naess, Stockholm, Sweden; Igor Nestrasil, Minneapolis, Minnesota; Lock Ngu, Kuala Lumpur, Malaysia; Paul J. Orchard, Minneapolis, Minnesota; Angela Schulz, Hamburg, Germany; Christoph Schwering, Hamburg, Germany; Elsa G. Shapiro, Minneapolis, Minnesota; Serap Sivri, Ankara, Turkey; Martha Solano, Bogotá, Colombia; Tima Stuchevskaya, St Petersburg, Russia; Elisa Teles, Porto, Portugal; Vanessa van der Linden, Recife, Pernambuco, Brazil; and Leonardo Vedolin, São Paulo, Brazil.

Declaration of Conflicting Interests

The author(s) declared the following potential conflict of interest with respect to the research, authorship, and/or publication of this article: Dr. Harmatz is consultant for BioMarin, Shire, Alexion, PTC, Ciesi, Armagen, Genzyme, and Inventiva. He has presented at symposia sponsored by BioMarin, Shire, Genzyme, PTC, and Alexion and has received honoraria from BioMarin, Alexion/Enobia,

Shire, Sanofi-Genzyme, PTC, Ciesi, and Inventiva. He receives grant/research support from BioMarin, Alexion/Enobia, Shire, Sanofi-Genzyme, and Armagen. Mrs. Meesen is an employee of Ismar Healthcare NV. Dr. Giugliani has received investigator fees, travel grants, and speaker honoraria from Actelion, Alexion, Amicus, Armagen, BioMarin, Genzyme, Lysogene, PTC, and Shire.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The expert meeting from April 28 to 30, 2016, in Stockholm, Sweden, the development and analysis of the premeeting online survey, and the writing of this manuscript were sponsored by BioMarin Pharmaceutical Inc. All authors received funding and travel support from BioMarin.

Supplemental Material

Supplementary material for this article is available online.

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