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Review article

The natural history of neurocognition in MPS disorders: A review

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ABSTRACT

MPS disorders are associated with a wide spectrum of neurocognitive effects, from mild problems with attention and executive functions to progressive and degenerative neuronopathic disease. Studies of the natural history of neurocognition are necessary to determine the profile of abnormality and the rates of change, which are crucial to select endpoints for clinical trials of brain treatments and to make clinical recommendations for interventions to improve patients' quality of life. The goal of this paper is to review neurocognitive natural history studies to determine the current state of knowledge and assist in directing future research in all MPS disorders. There are seven different types of MPS diseases, each resulting from a specific enzyme deficiency and each having a separate natural history. MPS IX, will not be discussed as there are only 4 cases reported in the literature without cognitive abnormality.

For MPS IH, hematopoietic cell transplant (HCT) is standard of care and many studies have documented the relationship between age at treatment and neurocognitive outcome, and to a lesser extent, neurocognitive status at baseline. However, the mortality and morbidity associated with the transplant process and residual long-term problems after transplant, have led to renewed efforts to find better treatments. Rather than natural history, new trials will likely need to use the developmental trajectories of the patients with HCT as a comparators. The literature has extensive data regarding developmental trajectories post-HCT. For attenuated MPS I, significant neurocognitive deficits have been documented, but more longitudinal data are needed in order to support a treatment directed at their attention and executive function abnormalities.

The neuronopathic form of MPS II has been a challenge due to the variability of the trajectory of the disease with differences in timing of slowing of development and decline. Finding predictors of the course of the disease has only been partially successful, using mutation type and family history. Because of lack of systematic data and clinical trials that precede a thorough understanding of the disease, there is need for a major effort to gather natural history data on the entire spectrum of MPS II. Even in the attenuated disease, attention and executive function abnormalities need documentation.

Lengthy detailed longitudinal studies are needed to encompass the wide variability in MPS II.

In MPS IIIA, the existence of three good natural history studies allowed a quasi-meta-analysis. In patients with a rapid form of the disease, neurocognitive development slowed up until 42 to 47 months, halted up to about 54 months, then declined rapidly thereafter, with a leveling off at an extremely low age equivalent score below 22 months starting at about chronological age of 6. Those with slower or attenuated forms have been more variable and difficult to characterize. Because of the plethora of studies in IIIA, it has been recommended that data be combined from natural history studies to minimize the burden on parents and patients. Sufficient data exists to understand the natural history of cognition in MPS IIIA. MPS IIIB is quite similar to IIIA, but more attenuated patients in that phenotype have been reported. MPS IIIC and D, because they are so rare, have little documentation of natural history despite the prospects of treatments.

MPS IV and VI are the least well documented of the MPS disorders with respect to their neurocognitive natural history. Because, like attenuated MPS I and II, they do not show progression of neurocognitive abnormality and most patients function in the range of normality, their behavioral, attentional, and executive function abnormalities have been ignored to the detriment of their quality of life. A peripheral treatment for MPS VII, extremely rare even among MPS types, has recently been approved with a post-approval monitoring system to provide neurocognitive natural history data in the future.

More natural history studies in the MPS forms with milder cognitive deficits (MPS I, II, IV, and VI) are recommended with the goal of improving these patients' quality of life with and without new brain treatments, beyond

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the benefits of available peripheral enzyme replacement therapy. Recommendations are offered at-a-glance with respect to what areas most urgently need attention to clarify neurocognitive function in all MPS types.

Contents

1. Introduction

The mucopolysaccharide (MPS) disorders are a group of lysosomal disorders in which specific enzymes responsible for the catabolism of glycosaminoglycans (GAGs) are absent or abnormal. As a result of this enzyme deficiency, accumulation of GAGs occurs in many organs including the brain. In most of the MPS disorders, there is abnormality in the brain documented by MRI imaging [1–4] and associated with a spectrum of neurocognitive and behavioral effects. In severe neuronopathic phenotypes, the disease is neuronopathic and progressive, with a course of relatively normal initial development, followed by a slowing in that development, a halting of further acquisition of skills, the loss of already acquired skills, and finally death. Even in the comparatively milder forms of MPS I and II, MPS IV, and MPS VI, the

brain may be involved, and the patient may function abnormally in neurocognitive ability and/or behavior, but the disease is not considered to be progressive or neuronopathic. As these diseases do affect the brain but are not progressive, it would be more precise to call them 'stable neuronopathic' forms. Natural history studies to determine rates of change and shapes of the neurocognitive trajectory are critical yardsticks to compare the trajectories of treated children.

The neuronopathic phenotypes are more prevalent than non-neuronopathic, such that about 2/3 of MPS patients have neurodegeneration. This decline, which involves not only IQ loss and skill regression, but in some types intense behavioral abnormality which affects the patient's life in a profound way as well as that of their family. Neurocognitive decline is a sensitive indicator of disease progression depending on appropriate measurement techniques [5]. Approaches to treatment of these devastating diseases are expanding and numerous clinical trials are active, many of them using measures of cognition as primary or secondary endpoints. Unfortunately, the data regarding the untreated disease course, so critically needed in a clinical trial for comparison to a treatment are often absent. In particular, neurocognitive assessment is not routine in the ongoing evaluation and management of these children, despite many recommendations in the literature [6–8]. The goal of this paper is to review the neurocognitive natural history data that exists, determine what variables might influence that natural history and make suggestions where additional studies are needed.

Neurocognitive tests provide information about how an individual's brain functions. While tests vary in adequacy of the normative data, measurement error, feasibility, and applicability to the patient sample [5,9], generally the validity of psychological measurement is comparable to the validity of medical tests [10]. However, adaptations to the patient sample, training and standard procedures, and other quality control procedures, are necessary to reduce measurement error and are reviewed elsewhere [5,9] Although specific tests useful in clinical trials are not reviewed here, other sources can provide up-to-date information [5,11,12].

There are seven different types of MPS diseases, each resulting from a specific enzyme deficiency and each having a separate natural history. Because MPS IX, deficient in hyaluronidase, has only 4 cases in the literature and no known cognitive manifestations, it will not be discussed in this review [13]. Although there are some overlaps, each of the six disorders to be reviewed has a different clinical presentation and a variable spectrum of severity. Data relevant to the natural history of each of these disorders is discussed separately below.

Since 2003, intravenous enzyme replacement therapies (ERT) have been developed for all but one of the MPS disorders. However, these approved treatments do not cross the blood brain barrier, and thus do not have substantial benefit to brain function [14]. The only treatment thus far that halts brain disease is hematopoietic cell transplant (HCT), the standard of care for MPS IH (Hurler Syndrome) since the mid 1990s [14,15]. Currently, gene therapies directed at the brain using AAV and lentiviral vectors, gene editing, protein fusion enzyme replacement, intrathecal and intraventricular delivery of enzyme and other treatments are in clinical trials [16].

The assessment of outcomes of brain treatment in these clinical trials are faced with two major challenges: knowledge of the natural history of the disease and finding sensitive measures of change. This review addresses the first challenge. Two articles address the second issue: the first consensus conference on neurocognitive outcomes [17] and a recent update [11] recommend measures that have been found to be sensitive and useful in clinical trials in MPS disorders.

2. Methods

This review of the neurocognitive and behavioral natural history studies in the MPS disorders will identify, by MPS type, the natural history studies, treatment outcome studies, and key investigations of predictors of outcome or disease course (e.g., mutation analysis, age of onset), and then indicate needs for more natural history data. Review of sensitive measures will briefly be mentioned in the context of the data quality and will limit comments to those measures that are related to neurocognition. While we will mention behavioral, adaptive, quality of life, and disability measures, which are also important in measuring disease progression, they will be discussed only briefly.

The content of this review is based on literature from Google Scholar and PubMed searches using search terms listed in Table 1 below. Searches were performed without date restriction. Publications were included peer reviewed journal articles, English language, empirical, human studies, that involved any assessment of neurocognition or developmental status. Published abstracts are also considered as emerging evidence. Additional publications were identified from reference lists within the most relevant MPS-related papers focusing on central nervous system function, pathophysiology, or clinical trial findings. The literature search was completed in May and repeated for updates in October of 2020. The studies cited were evaluated using the criteria presented in Table 2

3. Neurocognition: How is it Measured?

Before describing the literature on neurocognition in MPS disorders, it is critical to describe how it is quantified. Use of IQ-type scores (standard scores with a mean of 100 and a standard deviation of 15) have been used in many cases, but their limitations include an inability to separate children who are losing skills from those who are slowing in development [9]. Further, IQ-type scores cannot always be derived if a child's chronological age is greater than the age range intended for the test. In neuronopathic MPS disorders where functional levels are rather low, using a test that enables the individual to demonstrate skills is optimal, even if it is meant for younger people. In such a case, using the age equivalent score is the solution. Many studies have proposed age equivalent scores as the best way to examine the neurocognitive and adaptive growth of children particularly with neuronopathic disease, either over the course of the natural history or before and after treatment. Age equivalent scores are defined as the comparison of a child's performance to age groups whose mean or median scores are in the same range. In essence, it describes the mental age of the child in a particular domain or set of skills. Use of development trajectories based on age equivalent scores was first discussed in detail in a chapter by Shapiro and Klein [18] and subsequently expanded [8,19], clarifying that Hurler syndrome, or Mucopolysaccharidosis type IH (MPS IH) is

Table 1
Search terms for literature review.

Primary search terms	Secondary search terms
• mucopolysaccharidosis • Hunter, Hurler, Hurler Scheie, Scheie, Sanflippo, Morquio, Maroteaux Lamy, Sly • cognition • cognitive ability • intelligence • cognitive development • mental ability • attention • memory • visual spatial • language • motor development	• age equivalent • developmental age • Bayley or BSID • Wechsler • Griffiths • attenuated • neuronopathic • mutation • MRI, imaging • adaptive • behavior • quality of life • enzyme replacement • intrathecal • Intraventricular • enzyme replacement • HSCT and HCT, bone marrow transplant • gene therapy

Table 2
Summary of components evaluated in MPS studies of neurocognition and development.

Category	Relevant components	Comment
Characterization of study population	• severity of disease • subtypes • age • other demographics • how recruited • sample size	Studies that differentiate MPS type, and when feasible, phenotype, are more relevant Demographics including socioeconomic status are an emerging area of importance
Type of study	• prospective or retrospective • length of time of follow--up • clinical study vs clinical trial approach (e.g. recruitment by self--selection to a clinic vs. recruitment by specific parameters in a protocol)	Prospective studies are superior to retrospective studies in that the methods are uniform, planful, and likely to yield more complete and unbiased data to examine a specific set of questions
Methodology and measures used	• consistent use of measure in the trial for each patient, • appropriateness of the measure to the sample • appropriate metrics used to describe change over time • reliability of measure, • validity of measure for study population, • raters' experience/training	These factors will contribute to a more informative study which is less prone to bias.
Caretaker/parent involvement	• use of observational measures, • consistency of parental input (same informant each visit)	Many studies are not responsive to parental concerns, and do not address important endpoints such as behavior as well as cognition.
Other variables affecting neurocognitive and behavioral development	• genotypes • somatic measures (including history of hydrocephalus, epilepsy, and other brain involvement • MRI and other imaging • Biomarkers (both peripheral and in spinal fluid)	Understand the contribution of genotypes, somatic severity, biomarkers, and surrogate measures such as MRI will improve relevance of treatment response to particular groups.

neurodegenerative and that the neurocognitive decline is not the same as intellectual disability. The use of age equivalent scores is still challenging due to their less than adequate statistical properties in the very youngest children and in children over 6 [20] but they are useful clinically because they reveal the developmental status of the child [9]. Recently, test developers have understood this need and made available "developmental growth scores" which, unlike age equivalent scores, have equal intervals allowing a more accurate method for statistical analysis as well as clinical assessment [21]. This metric has not been used yet in studies of MPS disorders.

Recently the updated Consensus Conference on neurocognitive endpoints for MPS disorders indicated that "To capture disease progression and treatment outcomes, multiple metrics may be considered, including raw scores, age equivalents (where appropriate, considering the instrument and the impairment of the child) and standard scores." The guidelines continued that if a norm-referenced score above the floor is available, it is preferable to use this instead of age-equivalent scores for trial eligibility. In neuropsychological assessment, the standard for qualitative description of IQ findings where the normative mean is 100 and the standard deviation is 15, is as follows: scores within one standard deviation of the mean (i.e., 85–115) are in the "average range," scores 1–2 standard deviations below the mean (i.e., 70–84) are "below average," and scores more than 2 standard deviations below the mean (i.e., <70) are "impaired."

4. Natural History Studies of MPS Disorders

4.1. MPS I

Mucopolysaccharidosis type I (MPS I) is caused by the absence or deficiency of the lysosomal enzyme, α-L-iduronidase. Progressive accumulation of glycosaminoglycans (GAGs), heparan and dermatan sulfate, within the cells of various organs ultimately compromises their function [7] The severe form of MPS I (Hurler syndrome, MPS-IH) usually presents in infancy. If left untreated, worsening neurological, cardiovascular, and respiratory problems result in death in early childhood [7]. The natural history of the evolution of the somatic disease is well described [22]. Neurocognitive difficulties begin to emerge in the second year of life, with slowing of developmental milestones, then a halting of further development, and decline into the impaired range usually by age 4 years [20]. Neurocognitive decline separates those whose disease is neurodegenerative i.e., MPS IH from those with attenuated MPS I (MPS IA) [7] [23]. MPS IA originally was divided into two subtypes: Hurler Scheie, an intermediate form, with mild neurocognitive and learning difficulties and a mild form called Scheie syndrome with no neurocognitive impairment. However, this bifurcation has recently been supplanted with the view that there is a continuous spectrum of severity in MPS I [7]. For the present paper, we use the term MPS IA to refer specifically to patients whose neurocognitive course is attenuated, meaning that there is not rapid IH-type decline but rather there are neurocognitive abnormalities that do not necessarily worsen. As somatic disease can be significantly impairing of function and quality of life even for patients with intact IQs, we refrain from the term attenuated, instead focusing on neurocognitive course.

4.1.1. MPS IH-Hurler Syndrome

4.1.1.1. Hematopoietic Cell Transplantation (HCT) in MPS IH. MPS IH is the only MPS disorder that has a treatment for brain disease which is now considered standard of care [15]. Hematopoietic cell transplant was found to halt the progress of the brain disease in the 1990s. The first case report of a success in bone marrow transplant was published by John Hobbes in the UK [24]. In 1993, the University of Minnesota team reported success in maintaining neurocognitive ability in those children whose CNS impacts were not severely advanced (e.g., had an IQ of 80 prior to transplant) [25]. Eventually, IQ was supplanted by age at transplant as a better predictor of outcome in the first large series of cases [26,27]. The recommendation was made that children be treated before the age of 2 and with an IQ above 70 [27]. Subsequent studies confirmed the association of age at transplant with better outcomes [23,28]. Multinational evidence [15] indicated that HCT with matched related donors resulted in the best survival and lowest morbidity rates. Cord blood instead of bone marrow as the source of donor cells also had good outcomes [29]. Finally, the use of ERT (enzyme placement therapy) combined with transplant increased survival [2,30,31] and in one report improved neurocognitive outcomes as well [32]. Recent publications on the effectiveness of ERT as the sole treatment for patients with MPS IH [33,34] have indicated that it has little impact on neurocognitive function or neurologic status in comparison with hematopoietic cell transplant but may prolong life. Currently, transplant is the standard of care for patients with MPS IH; engrafted survival currently ranges from 79% to 90.3% at expert centers [15,31,35,36]. Lum [37] has pointed out that various conditioning regimens have different survival rates. Importantly, HCT is generally not available in developing countries [38]. Table 3 summarizes studies of neurocognitive outcome after HCT.

Table 3
Transplant outcome studies.

Reference	Date pub-lished	Study Population	Age range at baseline	Sample Size	Length of followup	Popula-tion studied	Survival rate	Cognitive measures	Cognitive Results	Metrics used to describe outcome	Hydro-cephalus?
Hobbs J.R., et al. *Journal of Inherited Metabolic Disease*. 1982;5:59-60.	1982	First BMT in Hurler patient	8 months	1	11.5 months		single patient survived one year	Griffiths Scale	Baseline Quotient of 77 and follow-up of 75	DQ	
Whitley et al. [25]	1993	All BMT with HLA identical donors	0.9-3.4 yrs.	11	3.8-8.9 yrs.	Diagnosed < age 2; HLA identical donor engrafted	82%	Baseline: Bayley Follow-up: WISC, Stanford Binet, WPPSI, Bayley	Patients with IQ >80 at baseline had a better outcome (within normal limits) than those below.	DQ/IQ and age equivalent scores (graphed)	1 shunted pre-HCT; 1 peri-trans-plant; None on follow-up
Peters et al. [26]	1996	All BMT with HLA unmatched donors	0.9 to 3.2 yrs.	40; 11 engrafted; survivors	0.7-5.1 yrs.	NIH funded BMT outcomes study at 14 North American centers	49%	Baseline: Bayley; Follow-up: WISC, Stanford Binet, WPPSI, Bayley	Children ≤2.4 years whose baseline MDI > 70 had a favorable cognitive outcome. Children whose baseline MDIs < 70 had a median age at BMT of 31 mos; those > 70 had a median age at BMT of 17 months	age equiva-lent scores (graphed)	none occurred
Peters et al. [27]	1998	BMT in HLA matched donors. GIS: genotypically identical; HIR: haplo-identical	0.4 to 7.9 yrs.	43: 30 engrafted; survivors	2.0- 13.9	NIH funded BMT outcomes study at 14 North American centers	GIS: 75% HIR: 35%	Baseline: Bayley; Follow-up: WISC, Stanford Binet, WPPSI, Bayley	No differences in neuropsychologic outcome between 18 GIS and 8 HIR survivors. Age at BMT: < 24 months significantly better slope than those with BMT > 24 months.	age equivalent scores (graphed) (Compared slopes for age groups)	none occurred
Vellodi, A., et al. *Archives of disease in childhood* 1997; 76: 92-99.	1997	10 HLA identical related, 16 non-identical related, 12 HLA identical unrelated	6 to 36 mos.	38: 13 survivors ≥5 years	2.4 -15.0 yrs.	BMT at 2 centers in the UK	55% survived, 34% engrafted; 26% cognitive data	Griffiths, British Ability Scales, WISC	None of the patients transplanted above the age of 2 are functioning at an 'acceptable' intellectual level…we would not recommend a transplant above this age.	Standard Scores were reported on multiple outcomes measures	Hydrocephalus noted at baseline but not mentioned on follow-up
Guffon, N., et al. *The Journal of pediatrics 1998;* 133: 119-125.	1998	11 had 13 transplants; 6 severe Hurler.	14 mos. to 8 yrs	11 patients; 10 survi-ved	1 to 10 yrs	Single center in France	9 had cognitive follow-up	Brunet Lezine, Terman Merrill, WISC-R	At follow-up 6 have a normal IQ (95 to 103). 2 have a borderline IQ (85 to 90). 1 borderline IQ (75). All have learning difficulties.	Standard Scores reported on multiple outcomes	Hydroceph-alus at baseline;
Souillet, G., et al. *Bone marrow transplantation 2003;* 31: 1105-1117.	2003	27; 21 Hurler; 13 HLA related; 17 unrelated	14 mos. - 8 yrs.	15 with cognitive follow-up; ≥3 yrs.	38 months to 16 yrs.	Single center in France	4 died; 85% survival	Brunet Lezine, Terman Merrill, WISC-R	Current IQs range from 77 to 105. Most in the normal range.	Standard Scores were reported on multiple measures	No hydro-cephalus at follow-up
Staba et al. [29]	2004	20 all with cord blood transplant	2-31 mos.	15/17 survivors cognitive follow-up	Median follow-up of more than two years.	Single US center	85% survival	Bayley, Mullen, Differential Abilities Scale.	After the initial post- transplant period of developmental delay, neurocognitive function stabilized or improved in all the children, and all have continued to gain skills.	Age Equivalent scores graphed	No reported problems
Lücke T. et al. *Developmental Medicine & Child Neurology*, 2007, 49:693-696	2007	5 with HCT	8-30 mos.	All 5 with develop-mental assess-ment	32 to 59 mos. with at least 4assess-ments	single center in Germany	all survivors	Denver Developmental Screening Test	No degeneration. Early transplant had better results but all children added developmental skills.	Age equivalent scores; DDST social skills, fine motor, speech, and gross motor	No hydro-cephalus reported improvement in subcortical white matter lesions.
Malm, G., et al. *Acta Paediatrica*, 2008: 97: 1108-1112.	2008	6 with HCT	11-22 mos.	5 with follow-up testing	12 to 68 mos.	single center in Sweden	all survivors	Griffiths	1-2 years post-HCT, some developmental delays in cognitive function followed by normalization of function. In five of 6, cognition normal, 1 patient below average.	Age equivalent scores were used	One patient had pre HCT hydrocephal-us shunted

Eisengart JB, et al. *The Journal of pediatrics.* 2013;162:375-80.	2013	9 with HCT + ERT and 10 with HCT only	18 mos ±6.8 in HCT+ ERT group; 17.1± 9.1 HCT only	19	2 yrs. follow-up	single center in US	all survivors	Mullen Scales of Early Learning	Short term cognitive benefits from ERT. Combined treatment lost fewer ELC points in 2 years compared to HCT only. Visual Reception, a nonverbal cognitive ability measure, showed most effects.	Standard Scores were reported	one patient with hydrocephal-us
Poe et al. [28]	2014	31 cord blood HCT. Age cohorts (2-8, 9-17, ≥18 months)	2.1 - 34.3 mos	31	2 to 21.7 years	single center in US	all survivors	Mullen Scales of Early Learning, Differential Ability Scales,	Younger age at transplantation was associated with improved cognitive function (p=0.001), receptive and expressive language (p = 0.004 and p = 0.01).	Age Equivalent scores were graphed (no scores); Cognitive ratio (DQ)	Not discussed
Aldenhoven et al. [15]	2015	217 engrafted patients divided into >85 and <85 at and >16 and <16 months at transplant	2-47 months	217	3-23 years	Medical records from multiple centers (inter-national) expert reviewers	all survivors	Not specified; many different instruments were used.	Combining predictors 'age at HCT' and 'baseline DQ/IQ' shows that 71.1% of patients with an age at HCT >12 mos. + a baseline DQ/IQ < 70 develop severe cognitive impairment (DQ/IQ <70) compared with 14.7% if the age at HCT is <12 months combined with a baseline DQ/IQ > 70.	Age equiva-lent scores + standard scores into normal (>85); mild (70–85); moderate (55–70); severe (<55)	No hydro-cephalus at follow-up but seen at base-line. Age at HCT predicts cerebral atrophy at follow-up.
Kunin-Batson et al. [40]	2015	47 engrafted; 34 from UK, 13 from U Minnesota	18.5 ±8.2 months	47	9± 6.7 yrs.	2 expert centers; UK and US	all were survivors	UK: Griffiths, WISC-III, and WAIS-III US: Mullen, WISC-IV, WASI, Stanford Binet	Linear regression analysis, adjusted for demographic and treatment factors, mutation severity associated with lower cognitive ability (p = 0.005) and Vineland (p = 0.004), but not QOL. Older age at HCT was associated with poorer physical QOL (p = 0.002); lower SES (p = 0.028) unrelated BMT associated with poorer psychosocial QOL (p = 0.010)	Standard Scores	Not discussed
Eisengart et al. [42]	2019	24; >6 months and <4 years; ≤4 previous doses of IV ERT; peri-transplant intrathecal ERT treatment.	16.3 ±6.17	24	1 - 2 yrs; 1 yr. n=18, 2 yrs. n=15	single US center	80% survival	Mullen, Bayley	Link between a biomarker treatment response and neurocognitive outcome. % decrease in nonreducing ends from csf from pretreatment to final intrathecal dose posttransplant was positively associated with % change in neurocognitive score from pretreatment to 2 yrs. Post-transplant. IT treatment safe and associated with decrease in CSF abnormalities	Standard Scores (IQs)	None occurred

4.1.1.2. Untreated Natural History. Although the natural history of MPS IH without transplant is known [20,34], clinical trials of proposed new treatments must now compare their results to the best results in transplant-treated children. While the sparse data from untransplanted children are no longer important for comparative studies, they provided important information about rate of decline, and the best metrics to measure outcome [20,23]. See Table 4.

4.1.1.3. Predictors of Neurocognitive Outcome. The relationship of severity of disease to mutation is more evident in MPS I than in other MPS disorders. Over half of patients with MPS IH who are homozygous for nonsense mutations (notably W402X and Q70X) show neurocognitive decline over time [39]. However, there are some patients who have the Hurler phenotype with other mutations, such as deletions or missense mutations. In a multicenter study of predictors of neurocognitive, adaptive, and quality of life outcomes of HCT [40], the strongest predictor of later neurocognitive impairment was mutation (e.g. being homozygous for nonsense mutations). For QOL physical outcomes, the age at transplant was critical. Low socioeconomic status and unrelated donors were predictive of poorer psychosocial quality of life (QOL) [40].

The challenge in newborn screening which is now occurring for MPS I, is determining whether patients without homozygous nonsense mutations are severe or attenuated [41]. Unless it is certain that newborns have the severe phenotype, the efficacy of a new treatment for MPS IH in a clinical trial cannot be determined.

While identification of severe disease by genotype can be determined in about 50%–75% of cases other markers are needed. Certain biomarkers, such as non-reducing ends in CSF heparan sulfate, may prove to be helpful [42], but so far this has not yet been sufficiently cross-validated. Other biomarkers as yet have not proven to be predictive of severe disease. Developing methods for early monitoring of patients whose clinical phenotype is uncertain is a high priority.

Another area of study is specific localization of brain damage in MPS IH. Although atrophy of the brain affecting the neuron itself is associated with age at HCT [15], dysfunction of the white matter appears to be a prevalent finding post-HCT [1,43]. It was initially thought that such damage was the result of the transplant treatment itself, but it is apparent that there is such abnormality in patients with attenuated disease with no history of HCT [44].

4.1.1.4. Summary of Long-Term Outcomes of Transplant in MPS IH. Studies reviewed in Table 3 have adequately demonstrated the effectiveness of HCT in halting neurocognitive decline due to MPS IH. These studies also demonstrate 1) the importance of early transplant to successful neurocognitive outcome and 2) the relationship of pre-HCT IQ to neurocognitive late effects. In addition, mutation type, severity of somatic disease, and changes in white matter volumes (especially corpus callosum) are associated with neurocognitive outcome.

These studies also find that HCT prevents hydrocephalus post-HCT, but does not prevent cord compression, dysostosis multiplex, cardiac complications, or carpal tunnel syndrome. Although steadily improving due to many factors, one of which is the addition of ERT to HCT protocols, HCT still has significant mortality. In addition, significant disability related to somatic disease, residual learning difficulties (inefficient processing and inattention), and psychosocial challenges remain.

New treatments must do better than HCT and must address these difficulties. For a new clinical trial, in addition to a comparison group of similar age and neurocognitive level undergoing HCT, outcome measures must include measures of somatic disease, disability and adaptive function, motor skills, attention and processing, psychological status, and interpersonal relationships.

4.1.2. MPS IA

We are using the abbreviation MPS IA to indicate patients with an attenuated neurocognitive course. Patients with attenuated MPS I often have severe somatic effects. Neither Scheie nor Hurler Scheie which are also in use, are appropriate as MPS is a spectrum and no real distinction can be made between them [6].

Although the studies presenting diagnostic and management guidelines for MPS I suggest yearly neurocognitive testing [7,45], little systematic neurocognitive study of MPS IA patients has been carried out. Most studies have been case reports and series of cases.

4.1.2.1. Case and Series Reports. Of the 8 single case reports found in the literature, only 2 mention IQ or neurocognitive impairment. In 5 observational studies with 3 or more cases, scores indicate less cognitive impairment in early treated patients using enzyme replacement therapy [46–50]. Another observational study found 2 of 29 patients below average in intelligence and 34% with language delay [51]. In another study of Mexican patients, 20% were cognitively impaired [52]. Ahmed et al. presents a group of 6 patients with a relatively severe mutation, L238Q, with a below average mean IQ of 74, compared with 6 patients with other mutations who had a mean IQ of 95 [53]. These L238Q patients also all presented with psychiatric problems. Note that of these studies, series of patients, only 5 report numeric findings.

4.1.2.2. Cross-Sectional Studies. A number of cross-sectional studies have been done examining neurocognitive function. Shapiro et al [23] found that 40% of 29 MPS IA were below average in IQ (<85) with genotype and somatic disease burden predicting their neurocognitive ability. IQ was relatively similar across age categories, suggesting stability over time. King et al. [44] found that smaller corpus callosum volumes in MPS IA were associated with decreased attention span; such an association was not seen in controls. These patients had low average ability levels compared to control values, with a mean IQ of 90.4. Ahmed et al. [54] found in a sample of MPS IA patients that the number of somatic symptoms increased with age and was associated with decreased IQ but not attention span. A few studies have correlated MRI abnormalities with cognition [55] and duration of disease [2]. Abnormal myelination on MRIs have been noted in MPS IA [1].

4.1.2.3. Enzyme Replacement Therapy. Prospective clinical trials of intravenous enzyme replacement therapy (ERT) have shown long term positive somatic benefits [56,57], but neurocognitive outcomes were not examined. New ERT treatments of MPS I led to the establishment of the MPS I Registry by Genzyme/Biomarin, now maintained by Genzyme Sanofi. The registry has fields that ask for neurocognitive impairment (yes/no) and neurocognitive test results [58]. Data in the Registry have been summarized [59]. As of 2014, there were 987 enrolled patients, 35.9 percent of whom were attenuated. Neurocognitive impairment was reported in 31.3% of Hurler Scheie and 9.4 % of Scheie patients, higher than expected numbers [59]. Seven of 76 Scheie patients were reported in the registry to have neurocognitive impairment [60]. A cautionary note about registry data is that results can be based largely on clinical judgment and less frequently test scores, creating some risk that somatic status influences the perception of developmental delay, such as when hearing impairment affects communication or carpal tunnel interferes with writing.

A single study has investigated intrathecal ERT to address neurocognitive impairment but found no beneficial effects over a two-year time period in six MPS IA patients [61]. However, a single case study of intrathecal ERT demonstrated benefits to attention [62].

4.1.2.4. Longitudinal Studies. Wraith et al [63] reported a prospective general longitudinal study of patients under 5 years of age. Of 16 patients, 4 had MPS IA and 12 MPS IH. The 4 patients with MPS IA showed normal mental development trajectories in the year that they were treated with ERT with the baseline age between 30 and 60 months. Ahmed et al [64] found that the six L238Q patients had severe neurocognitive and neurobehavioral deficits, but they were stable over 2 to 4 years, similar to the comparison group of 6 non-L238Q patients. Both groups showed increasing somatic symptoms with time,

Table 4
Untransplanted natural history data.

Reference	Date published	Study Population	Age range at baseline	N	Length of follow-up	How recruited	Survival rate	Cognitive measures	Cognitive Results	Metrics used	Hydro-cephalus?
Krivit W, Peters C, Shapiro EG. *Current opinion in neurology*. 1999;12:167-76.	1999	Hurler: No HCT or baseline prior to HCT	0-3	114	NA	Multi-center	NA	Bayley I or II	Decrease of one Mental Development Index (IQ) point per month	MDI (standard score) with mean of 100 and SD of 15. Floor of 50	Not mentioned
Wraith et al. [63]	2007	< 5 yrs old; 16 Hurler and 4 Hurler-Scheie-IV ERT for one year	0.5- 4.5	20	one year	4 European sites	NA	Griffiths Mental Development Scales	Hurler-Scheie patients had normal to above-normal rate of cognitive growth. Young Hurler showed cognitive growth but Hurler >2.5 years old did not.	Age Equivalent scores graphed	Not mentioned
Kiely BT, Poe MD, Escolar ML. *Molecular Genetics and Metabolism*. 2016;117:S67 (abstract).	2016	44 cognitive evaluations in 55 patients pre-HCT	<3 months to 32 months	44; 7 had >1 evalu-ation	NA	Single site	NA	Mullen Scales of Early Development	Cognitive function normal during first year but deviated from normal at 9 months. Overall showed lower cognitive functioning than typical.	Age equivalent scores	25% required shunt placement
Eisengart et al. [34]	2017	Follow-up of 23 ERT treated compared to 54 with HCT	ERT 0.5–4.7, HCT 0.4–4.8	23 un-treated, 18 ERT, 54 HCT	Up to 14 years	Multi-center	Survival HCT > ERT ERT> un-treated	Untreated & ERT patients died or too impaired for testing	Superior outcomes for survival and CNS pathology with HCT.	Survival plus neurological status (testing for those able)	More hydro-cephalus in ERT than HCT
Shapiro et al. [20]	2018	39 untreated only (overlap with Krivit, Peters, Shapiro 1999)	0-3	N=32; 7 had >1 evalu-ation	None	Multi-center	NA	Bayley I or II	For MDI <50, the range of DQs 13.3 to 61.5. Mean DQ age 1 to 2 years was 78.1 (S.D. = 17.7; N=19); age 2 to 3 years 64.5(SD 13.1, N=8); age 3 to 4 years was 56.3 (19.4, 6). Loss per year was 14 and 8 DQ points.	DQ as well as age equivalent score	No

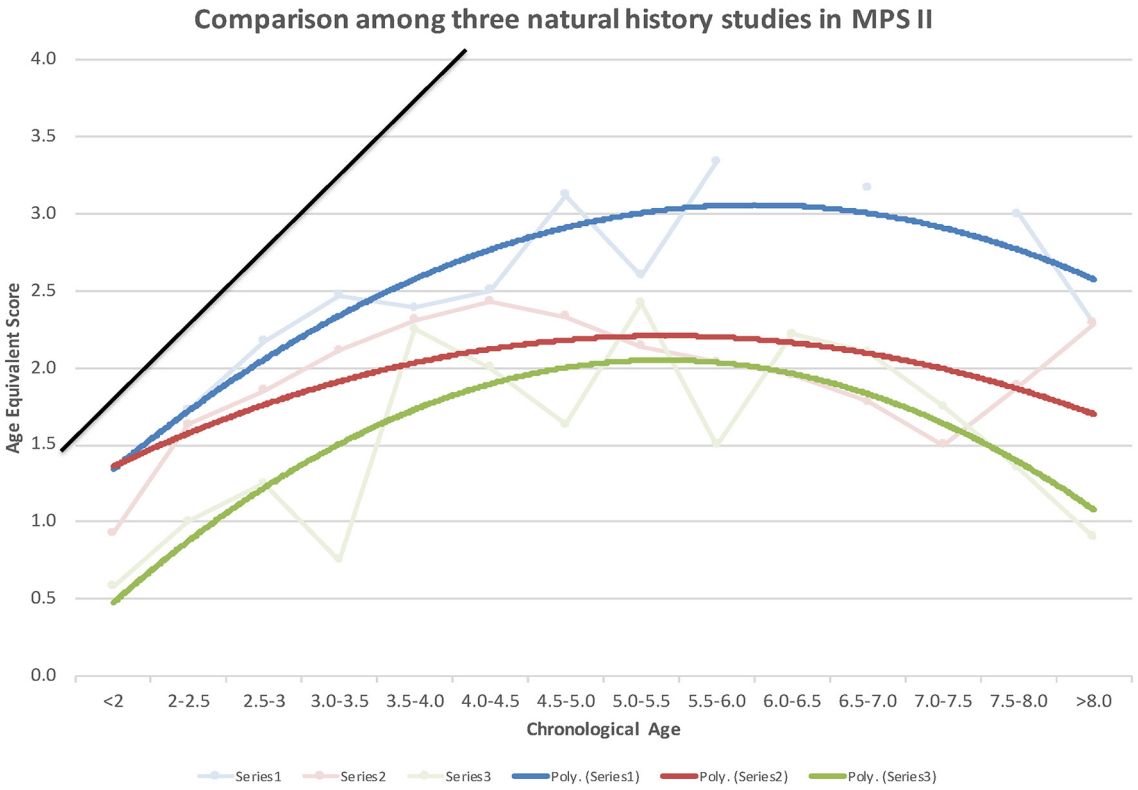

Fig. 1. Three Natural History Studies of Neuronopathic MPS II. Series 1 Young ID Harper PS. (1983). The natural history of the severe form of Hunter's syndrome: a study based on 52 cases. Developmental Medicine & Child Neurology 25: 481–489. Series 2 Seo S. et al. (2020). Natural history of cognitive development in neuronopathic Mucopolysaccharidosis type II (Hunter syndrome): Contribution of genotype to developmental course. Molecular Genetics and Metabolism Reports, 24:100630. Series 3 Holt JB et al. (2011) Natural progression of neurological disease in mucopolysaccharidosis type II. Pediatrics 127.5: e1258–e1265. Scores were medians by age group for each study.

but greater decrease in visual spatial memory and attention in the L238 group. Eisengart et al. [65] have preliminary data using the CANTAB, a suite of computerized neuropsychological measures, on 19 MPS IA patients, with a median of 4 visits per patient. Results indicate performance stable but well below the normative mean on measures of short-term memory, working memory, and rapid problem solving, consistent with the work of King et al [44].

4.1.2.5. Summary. A subset, about 20%–30%, of MPS IA patients are cognitively impaired. Cross-sectional studies show overall below average ability levels, poor attention span related to white matter abnormality, and reduced ability related to number of somatic symptoms. *Insufficient attention has been paid to the neurocognitive abnormalities in MPS IA, and therefore to possible treatment approaches.* Early treatment with ERT appears to have some neurocognitive benefit, likely due to the amelioration of somatic symptoms. While there are negative results for a group of patients treated with intrathecal enzyme, the authors raised the possibility of a much slower rate of deterioration in this phenotype, such that the present length of this trial could not illuminate benefit. Other treatments that may benefit brain function are now coming on-line, and it will be important that trials consider the potential for protracted time to show benefit. With no definitive longitudinal studies, and no indications of sensitivity to change nor time to deterioration, it will be difficult to assess treatment outcomes. Thus, there is a significant need for more longitudinal studies, especially given the rarity of the attenuated form of MPS I.

4.2. MPS II (Hunter Syndrome)

MPS II is a multisystem disease, affecting almost all of the organs of the body. Death occurs typically in the second decade for patients with severe disease, and recent data and for milder disease, recent data in patients treated with ERT finds that survival is longer, some up to the fifth or sixth decade [66,67].

It is the only X-linked MPS disorder and it results from heterogeneous mutations of the iduronidase-2-sulfatase gene [68]. Serious somatic symptoms arise due to depositions of glycosaminoglycans in many organs of the body, but there is heterogeneity in the clinical phenotype [6]. The most common physical problems are hearing loss, airway disease, dysostosis multiplex, hepatosplenomegaly, facial dysmorphia, cardiac involvement, and carpal tunnel syndrome. MPS II is variable in age of onset, severity, and rate of progression of somatic symptoms [68]. Although usually diagnosed at ages 2 to 4, slightly later age than MPS I, some perspective on early disease manifestation is offered in a series in which all but one of the 8 patients in a series were diagnosed at under one year of age by having a relative with the disease [69]. These infants all showed symptoms such as hernias, hepatosplenomegaly, coarse facies, and skeletal abnormalities that might have not otherwise been linked to MPS II, suggesting that disease processes are operating earlier than previously thought. Neurocognitive outcomes were too early to determine.

Of all the MPS disorders, MPS II has the greatest uncertainty about the neurocognitive progression of the disease. It has been classified into two forms: a severe neuronopathic form with a major effect on neurocognitive function, and an attenuated form thought to have little or no neurocognitive consequences [70,71]. Like other progressive MPS diseases, development is initially normal, followed by a period of plateau, and then decline [19]. Initially MPS II was thought to be similar to MPS I, but the onset of neurocognitive slowing has been found to occur later; mostly between ages 2 and 4 [19,72]. Significant variability in the age at developmental arrest has been observed [73,74]. Decline is even more variable; Martin et al. [72] describes it from 5 to 8, consistent with the findings of Seo et al [73]. Recent examination of neuronopathic MPS II patients suggests that a plateau in development (staying at a low

functional level for months or years before ultimate decline) occurs in some patients [75,76]. In fact, some may never decline and could be classified as nonprogressive neuronopathic patients. (See further discussion below). Thus, MPS II appears to have a wide and variable spectrum of severity.

Central nervous system problems in MPS II apart from neurocognitive impairment include behavioral impairment, communicating hydrocephalus, seizures, sleep apnea, and spinal cord compression [77] [59]. A higher risk for hydrocephalus [72] and seizures in the later stages of the disease [78] may exacerbate neurocognitive decline but this has not been studied. However, in their follow-up study of 27 patients who had ERT treatment, Tomanim et al. [79] found 7 patients who had seizures, all of them with neuronopathic disease. Hydrocephalus was found in only two patients in this cohort. Although 2/3 of patients have the severe form of the disease [80] those with the attenuated form may also have neurocognitive difficulties, with contributing factors of hydrocephalus (although rare), hearing loss, and other somatic problems [81]

4.2.1. Mutations and Cognition

Assessing severity is further complicated by variable genotype-phenotype correlations, primarily because of the many 'private mutations' peculiar to extended families [68]. Deletion, recombination, and frameshift abnormalities usually have a severe phenotype [82]. Null mutations are also usually associated with severe disease, although some have been found to be associated with intermediate or attenuated forms. Although most missense mutations are associated with the attenuated form, about a third may be associated with neuronopathic disease [82]. Deletions, recombinations, and frameshift abnormalities usually have a severe phenotype [82]. In the data in that study, 16 of 41 patients (39%) had one of these abnormalities. Null mutations are also usually associated with severe disease, although some have been found to be associated with intermediate or attenuated forms. Although most missense mutations are associated with the attenuated form, about a third may be associated with neuronopathic disease [82]. Thus, prediction of phenotype from genotype is uncertain in less than half the cases, making it difficult to predict the developmental course of the disease in a clinical trial.

Another factor that complicates the understanding of severity of disease is the lack of precise definition of phenotypes. Many of the studies of genotype-phenotype correlation state that the severe patients exhibit cognitive impairment or neurocognitive decline, while the attenuated patients have 'normal' neurocognitive development, though intermediate phenotypes are occasionally mentioned without specific criteria. Although a few studies have used neurocognitive assessment to make categorizations [83–85], most studies do not, and are thus subject to clinical bias and lack of standard methods. A single study has described the criteria for the intermediate forms, having mild or moderate learning disabilities and less severe skeletal disease [86].

In 1993, Bunge [87] reported mutations in 16 patients with notations regarding their clinical severity. This was followed in the later 1990s by several additional reports of mutations and associations with clinical judgments of severity [86,88–90]. Recent literature has many more such reports. However, the far the only paper with actual measurements of IQ and relationship to mutation was Froissart et al [83]

The lack of rigorous, generally accepted criteria for severity is well documented in a study of outcomes of ERT treatment in the UK [76]. The authors state that a binary classification of neurological outcomes does not fit their patients. They suggest that there is a third group of patients, with intellectual impairment but who do not fit the progressive neuronopathic disease category and instead are stable over an unspecified period of time. Further research is needed to clarify whether this is lifelong or whether they eventually decline.

Enzyme replacement therapy was approved in 2006 [91]. Elaprase has been found to improve the somatic aspects of MPS II, but because it does not cross the blood brain barrier, it does not treat the neurocognitive and behavioral deficits. Hematopoietic cell transplant has been tried with mixed results. New treatments, either in clinical trials or proposed, include intrathecal enzyme, protein fusion enzymes that cross the blood brain barrier, and gene therapy. There are two significant challenges in treatment studies. First, early identification of the patients with the neuronopathic phenotype is not very accurate. Second, even if the patients can be confirmed to be neuronopathic, the variable course makes it difficult to select the window of time in which a treatment effect can be detected.

4.2.2. Natural History Studies of MPS II

The first notable retrospective natural history studies of children with MPS II were carried out by Young et al [92] in 1982. They divided 88 patients into two groups - severe and mild - using age equivalent scores on various IQ tests. 24 had relatively normal intellectual skills; the rest could be divided into those who were already impaired by 2 to 4 years of age, and those who showed progressive decline. In a second paper [70] they delineated the differences in disease course between the severe and mild forms in 52 patients, noting severe behavioral problems in the severe form contrasted with the lack of such behavioral disturbances in the mild form. They noted that both groups had cardiac and respiratory problems and hepatosplenomegaly.

4.2.3. Cross Sectional and Retrospective Studies

A 77-subject Brazilian study [78] delineated several important points: an earlier onset of the severe form than the attenuated forms, the association of neurocognitive and behavioral abnormalities in the severe form, and onset of neurodegeneration between 4 and 10 years of age. CSF GAG levels and heparan sulfate levels appeared to be higher in patients with neurocognitive impairment versus patients with cognitively intact MPS II [93]. Fan et al. [94] found that in 16 MPS II patients, 10 with neurocognitive impairment, distinctions could be made with respect to decreased brain tissue volumes, with changes evident as early as 7 years of age. (It should be noted that slowing of neurocognitive growth and decline in some patients start well before that age). Ibanez [95] administered the Griffiths Scale of Mental Ability to six Colombian patients between ages 6 and 10. Their locomotion ability (gross motor ability) was in the average range. The lowest score was hearing/language was below average; while the other three scores (personal social, eye-hand coordination, and execution) were at the borderline/low average level. It was not stated whether these patients were neuronopathic or attenuated, although it was stated that two of them were functioning at a higher level. Without more details about individual performance, averaged scores with this small N are not meaningful.

Following on from Young and Harper's papers [70,92,96], Holt et al [71,74] published two important papers, one retrospective-longitudinal (see below) and one predictive. The latter documented the neurocognitive, behavioral, clinical/somatic, and motor abnormalities of both neuronopathic and nonneuronopathic patients with a consistent protocol. This study of 49 patients over 151 visits found that 37 patients showed neurocognitive decline. Those with CNS abnormality were diagnosed at a mean of 3 years and had their initial visit at 5.5 years, while those with milder disease were diagnosed at slightly over 3.5 years and were seen for their initial visit at 8.5 years. They identified seven early developmental difficulties associated with later neurocognitive dysfunction: increased activity, behavioral difficulties, seizures-like behavior, problems sleeping, perseverative chewing, and lack of bowel and bladder training.

4.2.4. Longitudinal Studies

Holt et al.'s retrospective-longitudinal study was a detailed investigation to elucidate their natural history of MPS II [74], in which 50 patients were studied for 152 visits. They were administered the Mullen Scales of Early Learning and the Scales of Independent Behavior. Age equivalent scores were plotted to demonstrate the differences in developmental trajectories between the neuronopathic and

nonneuropathic patients. Neurocognitive, adaptive, language (receptive and expressive) and motor skills (gross and fine) were examined. Patients could be separated easily by age into the two severity groups, except in motor skills. Motor skills were similar in both groups, peaking between 48 and 55 months and then declining after 72 months. Neurocognitive performance increased steadily from early years in the non-neuronopathic group. The neuronopathic trajectories are more complex, as inferred from the graph of the Mullen Early Learning Composite. There was only one patient who was followed from normal early development through slowing and decline. One other patient was below average at a little over 5 years of age and then, seen two years later, had not developed further and was significantly impaired. Those who were clearly neuronopathic were already at a very low level by age 6 at their initial visit, with most functioning at a 2–3 year-old level. One can infer from these results that the halting of further neurocognitive development likely occurs between 2.5 and 5 years of age. Further information is needed to clarify this trajectory.

Seo et al [73] collected longitudinal data on 13 MPS II ERT-treated Japanese patients, with defined mutations, on the Kyoto Scale of Psychological Development (the standard developmental cognitive measure in Japan). For the group as a whole, development ceased after 36 to 42 months. The mean age equivalent was the same at 3 years of age as it was at 6 years. Children with missense mutations maintained development for a significantly longer period than those with deletions, recombinations, or null mutations. It was noteworthy that 2 patients were under two years of age and 5 were under three years of age at initial visit.

Another important aspect shared by the Holt and Young and Harper data [74,96] is the long period of stable very low-level functioning as measured by age equivalent scores, without further decline, in these patients. As described above, intermediate patients that are neuronopathic but maintain a steady level of neurocognitive impairment for many years may be a contributory factor to the rather gradual MPS II curves, which are not as steep in MPS I and MPS III.

These outcomes of the previous three studies are compared in Fig. 1. In series 1, the relatively higher functional level may be due to the multiplicity of tests used in those patients (Griffiths, Merrill Palmer, Terman Merrill, Stanford Binet, and Vineland) many of which are primarily nonverbal. In Series 2 only the Kyoto Scale of Psychological Development (KSPD) was used, including language as well as nonverbal skills. In Series 3, the Mullen Scales of Early Development was used, including language. The relatively low scores in the Series 3 probably reflects the ascertainment bias in referrals to a single expert clinical center. Note that for Series 2, this reflects a combination of two mutation classifications for neuronopathic MPS II. Those patients with deletions, rearrangements, and nonsense mutations had a significantly steeper downhill course on the KSPD than those with missense mutations. This distinction is not shown in this graph.

4.2.5. Prospective Longitudinal Study

A preliminary report by Muenzer et al [97] of a prospective longitudinal natural history study carried out prior to a clinical trial of intrathecal enzyme reported standard scores on the Differential Abilities Scale II using the GCA (General Cognitive Ability) index. In a sample of MPS II patients with baseline above 55, the mean baseline GCA was 78.4 (S.D. 19.11). Mean change in 27 patients was -0.9 over 12 months and -3.8 over 24 months for 20 patients, suggesting stability; however, GCA scores varied widely, with some experiencing rapid declines. Because these were standard scores and on a different type of measure, they could not be compared to previous natural history data. However, the findings of the slow decline of MPS II patients as a group are consistent with other studies and with the possible inclusion of patients with an intermediate phenotype. The publication of more definitive findings from this study is anticipated.

4.2.6. Treatment studies

4.2.6.1. Hematopoietic Cell Transplant. Unlike in MPS I, the results of transplant in MPS II are equivocal.

Most case reports found benefits for somatic symptoms and for activities of daily living; but for neuronopathic patients, stabilization of IQ was not found. Kubaski et al. used questionnaire data and measures of activities of daily living (ADLs) and found some improvement in somatic disease and in ADLs with HCT compared to ERT, but no direct measures of cognition were used [98]. Guffon et al. [99] and Vellodi [100] found improvement in somatic symptoms but did not find benefit for the neuronopathic patients on measures of IQ. Selvathan et al. [101] presented 4 cases with scattered IQ results, asserting that HCT may stabilize disease course early in the course of the disease. In the largest sample, Tanaka et al. [102] suggested that they had good results in their patients; however, in the 11 patients who were given IQ tests, decline was noted except for one who was stable over time. Many of these studies suffer from lack of quantitative IQ data and other comparative data that would provide expectations for the neurocognitive course of the disease for each patient. The benefits of HCT for cognition are still in doubt for MPS II, although many investigators have claimed benefit from early treatment.

4.2.6.2. ERT. This treatment was approved in 2006, and most children have shown benefit for somatic symptoms. With the 6 minute walk test (6 MWT) as a clinical criterion for improvement in the first studies [84], early ERT treatment has been found to correlate with better but not normal development in case reports of neuronopathic patients [80,103,104]. From the Hunter Outcome Survey sponsored by Takeda [105] a summary of the neurocognitive outcomes in 626 patients based on the clinical impression of the attending physician were: normal approximate (IQ >80, 38%), borderline (IQ 70–80, 10.9%), educable (IQ 50–70, 8.6%), trainable (IQ 30–50, 15%) or profoundly impaired (IQ <30, 27%). 61.5% suffered some extent of neurocognitive impairment. Note that these data include all forms of MPS II.

4.2.7. Attenuated (Non-Neuronopathic) MPS II

While the standard nomenclature currently being used call such patients 'non-neuronopathic,' evidence reported below suggests that there is brain involvement with functional impairments in these patients. Thus, as in MPS I, attenuated may be a better description. Relatively little information is available about the natural history of the attenuated MPS II patients. Their somatic and neurocognitive status were first described by Young and Harper [106]. They have significant life-threatening somatic difficulties and some CNS challenges such as cord compression and hydrocephalus. Hydrocephalus and other brain abnormalities that can affect learning and behavior [6,80]. Even children who do not regress can show neurocognitive difficulties [75], poor adaptive skills [107–110], and attention difficulties [81]. A study by Ahmed et al [54] that included 14 MPS II patients used a measure of somatic burden of disease, and found a positive correlation between number of physical symptoms and age but not IQ or attention. However, the MPS II patients had below average scores on attention measures. Kuratsubo et al. [111] in a study of 10 patients in Japan who were classified as attenuated found that Wechsler testing indicated that only 3 were in the normal range (above 85) in either Full Scale IQ or Verbal IQ (used for two patients with visual disturbance). All had IQs above 55. Psychological disturbance apparently was correlated with IQ; the lower the IQ the more likely the disturbance. It would seem that some of these patients had an 'intermediate' phenotype with low but stable IQ.

Yund's study [81] compared 20 patients with attenuated disease to normal controls or normative data. IQ and memory were found to be within normal limits in these patients, while measures of attention were one standard deviation below the average range. Somatic burden of disease was negatively associated with attention and volumetric

measurements of corpus callosum and cortical white matter were positively associated with attention. Yund recently reported [112] preliminary results from a longitudinal analysis of a subset of the 20 original patients. Attentional performance was below average and did not improve over time. Organization/rapid problem solving and visual short-term memory (for patterns or spatial arrangement) were each at the lowest end of the average range. Working memory and problem-solving tasks remained stable. Higher scores in spatial working memory, organization/rapid problem solving, and short-term memory for patterns were associated with higher psychosocial QOL

The only published study of MPS II patients [107] examined emotional adjustment, quality of life, and adaptive function in 15 patients as well as IQ and somatic disease burden. IQ increased slightly over time in these patients, but daily living skills were more impaired and decreased over time in tandem with increase somatic disease burden. This was similar to the findings of a questionnaire-based study by Needham et al [108] which found similarly that the milder patients still had difficulties in daily living skills: more than one standard deviation below the mean but far better than the severe group whose scores were more than three standard deviations below the mean.

Finally, Crowe et al [113] examined detailed neurocognitive/neuropsychological data as well as behavioral profiles of 3 attenuated male patients, at baseline and at one- and 2 years-post ERT treatment. They found that some executive functions, especially on measures of planning and organization were impaired, despite ERT. Generally, their results corroborated the larger study of Yund [81].

4.2.8. Summary

From the few studies done, no clear criteria can classify mild, intermediate and severe forms of MPS II. Differentiating the attenuated and stable neuronopathic patients from those with severe and progressive disease in studies through detailed neuropsychological, adaptive, and genetic information will provide better comparisons for clinical trials and for understanding clinical prognosis. Mutation analysis may provide a tool to differentiate various developmental trajectories [68,73]. Recent studies have shown different patterns of progression depending on mutation type [73]. Prospective natural history studies need to include 1) neurocognitive levels (age equivalent scores for all young and impaired patients), 2) somatic severity level, 3) other assessments of neurocognition including attention and executive function in those functioning at a level high enough to measure, 4) detailed genotype studies, and 5) treatment status including age at onset of treatment.

4.3. MPS III Sanfilippo Syndrome

Of the mucopolysaccharidoses, MPS III or Sanfilippo syndrome is the one that can be described as not only neurodegenerative, but also as a childhood dementia. Even though that term carries with it negative connotations, its value lies in describing a disease whose symptoms are primarily neurological with both neurocognitive and behavioral aspects [114] and draws attention to the relatively rapid and devastating decline in function and family burden that this disease causes [115,116]. MPS III is caused by low or absent production of enzymes that are required for heparan sulfate metabolism. Four subtypes, A, B, C, and D results from the absence of four different enzymes with an overall prevalence of one in 70,000 [117]. All are progressive and ultimately lethal but have a different time course. The enzyme that is deficient in MPS IIIA is heparan-N-sulfatase (SGSH), in MPS IIIB it is α -N-acetylglucosaminidase (NAGLU), α-glucosaminidase acetyltransferase (HGSNAT) in MPSIIIC, and N-acetylglucosamine 6- sulfatase (GNS) in MPSIIID.

4.3.1. Early Studies of Cognition and Behavior

Sanfilippo syndrome, first described in 1963 [118] drew very little attention at first, and was thought to be a variant of Hurler syndrome. In an early paper, delayed development was described with regression in 9 cases, along with aggressive and destructive behavior, unusual facial features, and diarrhea [119]. Van de Kamp et al [120] described phenotypes in 73 patients (with clinical data from 64). Dementia with loss of acquired functions, was described for all patients, but noticed earlier in type A. A graph of IQ vs age was the first to demonstrate the downhill trajectory in these patients on neurocognitive tests. In this same study, behavioral disturbances and somatic changes were described, but with significant heterogeneity especially in type B [120].

In 1983, Nidiffer and Kelly [121] sent out a questionnaire to parents of MPS III children to elucidate the acquisition and loss of neurocognitive and social/adaptive milestones, and behavioral abnormalities. This first compilation of the development and decline of children with MPS III was compared with a group of typically developing children. A uniform behavioral syndrome was described, including a loss of skills at around age five and later loss of ambulation from 11 to 13 years of age.

Cleary and Wraith [122] described clinical details of 62 patients with severe neurodegeneration accompanied by serious behavioral disturbance, but with a mild somatic phenotype. For the first time, they detailed the evolution of the disease into three phases. In the first phase until the age of 3, developmental problems are mainly noticed in language. During the second phase starting from ages 3 to 4, behavioral disturbances become prominent including hyperactivity and aggression, together with sleep disturbance. After 10 years of age, the third phase includes joint stiffness, impairment of mobility, and feeding difficulties, aspiration, and sometimes seizures. They note a few cases with attenuated phenotypes.

Barone et al. [123] described three cases of IIIA in which MRIs were obtained at baseline with a follow-up of 3 years. Neuropsychological testing was done on two patients at 20 months before noticeable onset of neurological symptoms and then again at 3 ½ and 4 ½ years with IQs of 30 and 44 respectively on the Terman-Merrill test. MRI showed atrophy and myelination delay before the onset of neurological symptoms and worsening at follow-up, but a patient with more severe neurocognitive impairment had less severe MRI changes. For the third patient, who was seen initially at 12 years of age with type B, severe intellectual impairment[1] and absence of communication was accompanied by severe cortical atrophy, with little change three years later. The authors concluded that MRI abnormalities may precede the onset of overt symptoms in MPS III but are unrelated to severity of phenotype.

Meyer et al. [124] proposed a questionnaire-based Four Point scoring system (FPSS) for Sanfilippo syndrome based on the assessment of 71 MPS IIIA patients, 14 patients with IIIB, and 4 patients with IIIC. Motor, Speech and Cognitive functions were rated on a four-point scale as well as a Total score based on information provided by family, doctors, teachers, and therapists. This system was designed to follow the course of individual patients and to classify the rapidity of the disease process.

4.3.2. Predictors of Severity in MPS IIIA

MPS IIIA is the most common subtype. Mutation analysis has sought to define a genotype-phenotype relationship, classifying children by age of onset and rate of progression. As a result, slow progressing attenuated phenotypes have been identified in contrast to the more common rapid progressing type. While most studies classify the rapidity of progression using undefined clinical judgment, only a few studies have employed neuropsychological testing. Common mutations associated with rapid progressing disease (R245H and S66W) were first described in Dutch and Italian samples in 1998 [125,126]. More than half of the patients have common mutations which showed definitive regional prevalence [127]

[1] This paper used a discontinued term, "mental retardation," which is nonspecific and may have indicated either cognitive impairment or neurodegeneration, but the intended meaning is not clear from the text. We do not carry the term forward as it is not considered an appropriate descriptor of intellectual status.

4.3.3. Slow Progression and Attenuated Patients

We distinguish between slow progressing and attenuated MPS IIIA. The literature describes patients who have relatively normal intelligence who we call attenuated, and those who are severely impaired, but may show slow progression or even no decline, who we call slow progressors.

Since most cases are rapid progressing, identifying and gather natural histories on those who are slow progressing has been a challenge. All of the studies described below have some sort of neuropsychological testing to document slow progression. Gabrielli [47] documented a stable IQ in a 20-year-old patient with a R206P mutation from age 6 (IQ 43) to age 20 (IQ 45). The S298P mutation was described in detail in 7 of 54 patients using the FPSS to document slower course of decline [124]. Similarly, 10% of alleles in German patients with MPS III had this slow progressing mutation [128]. Two of 25 patients recruited for a natural history study had this mutation [129], also with a slow progression of disease. Recently, a few severely impacted, rapidly declining patients also have been described with this mutation, thus the prevalence and natural history of this variant needs further exploration (personal communication, Samantha Parker 2020).

Seven attenuated MPS IIIA patients in the Netherlands were reported by Nijmeijer et al. [130]. These patients were identified by family screening and had normal intelligence (N=7; 4 of had neuropsychological testing with normal IQ and missense changes (S298P and R74C). The patients, often with retinal dystrophy and cardiomyopathy, showed late onset neurocognitive impairment or no impairment at all.

DiNatale [131] found two second cousins with MPS IIIA, both with E369K, a reported mild variant. On the second allele, one had with R433Q with a severe form of the disease and the other, P128L, attenuated. Using neuropsychological testing, the severe patient diagnosed at age 5, functioned at 6 months mental age equivalent on the BSID at age 12. The attenuated patient, diagnosed at age 13, functioned at 3 years of age on the WAIS (IQ 50) at age 18. It was also suggested that the presence of an R456H polymorphism could be related to the severe disease in the younger patient. Note that an IQ of 50 at age 18 is in the range of moderate to severe neurocognitive impairment, which reflects a lack of clarity about what the description of 'attenuated' means and the complexity of predicting neurocognitive outcome based on mutation alone.

4.3.4. MPS IIIA Summary

While most patients have the severe form of MPS IIIA, the attenuated form appears to have a wide spectrum, from a slow progressing but nevertheless relentless form to a group of patients in the Netherlands with little neurocognitive abnormality until later in life. Similar to the contemporary trend away from using the term "attenuated" in MPS II, we propose consideration of terms for MPS III that reflect onset or velocity of dementia processes, rather than severe or attenuated. While mutation type is helpful to separate these patients from the rapid progressing group, it is insufficient to fully characterize the disease. Only a handful of published studies have measured evolving neuropsychological function using systematic neuropsychological testing to investigate genotype/phenotype correlations [47,131].

Diagnosis after the age of 5 years of age can be another predictor of speed of decline. Later diagnosis was associated with a slower course of disease in 3 European countries and was a reliable indicator of disease severity [132] supporting the assertion that age at diagnosis could be used to predict disease course. This was confirmed by a natural history study [129]. However, it should be noted that age at diagnosis may be influenced by the familiarity of the clinician with the disease, misdiagnosis, or lack of available testing.

Yogalingam [133] pointed out the necessity of careful measurement of patient phenotype recording the natural history of the syndrome in the individual patient. He also advocated accurate measurement of urine GAGs to predict the severity in each genotype. However, presence of polymorphisms and private mutations may be obstacles to accurate predictability of severity [127,133].

4.3.5. Predictors of Severity in MPS IIIB

Early description by van de Kamp [134] suggested that uncomplicated 'mental retardation' was the predominant finding in MPS IIIB with behavior problems less frequent in those who had an attenuated course. Subsequent studies have not entirely confirmed this early description, as the neurocognitive decline with behavioral problems seen in IIIA has also been described in MPS IIIB [135,136]. Well over 100 mutations have been reported in IIIB, [137] most being missense mutations with a very low frequency of each mutation. The majority of mutations are unique to individual families resulting in a wide spectrum of clinical phenotypes [133,138–140].

The attenuated form of the disease occurs frequently in the Dutch populations [134,140,141] which suggests a founder effect. Valstar [142] reported that only 9 of 44 of Dutch patients had the severe form, with slow progression and stagnation of development in the mutations R643C, S612G, E634K, and L497V, a quite different course than in the other patients. Moog [143] reported on 20 patients with attenuated MPS IIIB who had very slow progression and lived to adulthood despite presenting early in life (all had developmental delay before age 10) with neurocognitive and behavioral difficulties. All but one living patient were in institutions for individual with intellectual disability; average age at death in this group was 56. Only two had mutation analysis and were found to be homozygous R643C. In the Nijmeier paper described above [130] of 15 late-onset patients, only one patient with IIIB was identified; he was heterozygous for the R643C gene with a WAIS-III Full Scale IQ of 68 at age 26.

Lin [144] reports IIIB to be the most common type of Sanfilippo syndrome in a Taiwanese population, with little phenotype/genotype association. It should be noted that the R565W is the most common variant. In Asian populations, an attenuated progression with heterozygous presentation of R565P has been found only in Okinawa, [145] suggesting a founder effect [146]. When the variant was homozygous, it was found to be severe. High clinical variability may be due to allelic heterogeneities of the NAGLU gene [147].

4.3.6. MPS IIIB Summary

To conclude, the problem in IIIB, like IIIA, is establishing definitions of what constitutes 'attenuated' disease. Is it the same as slow progressing but nevertheless lethal in the 2nd and 3rd decade? Or does it mean adults with or without cognitive impairment, either showing dementia or not? However, despite the uncertain definition for attenuated disease, the description of the IIIB patients with *severe* disease suggests a consistent decline of cognition and behavioral difficulties, but like IIIA, some are rapid and others slowly progressing. Identifying these patients by age at diagnosis or at first symptom emergence may result in better predictability. Also, a few identifiable mutations in the attenuated forms can be identified such as the R643C mutation and perhaps the R545W when heterozygous.

4.3.7. Natural History Studies of IIIA and IIIB

Detailed natural history studies of neurocognitive development were published starting in 2010 but no prospective longitudinal studies were reported until 2014. Because often these earlier studies combined both MPS IIIA and B, they will be reviewed together.

4.3.7.1. Cross Sectional Studies. Malm [148] found Type A most common in Sweden, in a retrospective cross-sectional study of 22 patients, based on medical records. Early speech development was delayed in half of their subjects, who had normal gross motor development. Later behavioral problems emerged along with developmental delay. Neurocognitive testing was done by the schools without reporting exact scores but categorizing their mental ability; 7 patients showed mild and 5 severe 'mental retardation' on entering school.

Valstar [114] examined 73 MPS III patients, 39 of whom could be tested as their developmental function was over 3 months of age. They were recruited from 4 Dutch diagnostic centers. Using the BSID-2 or Snijder-Oomen (a nonverbal test), or the WISC-III, they found a maximum developmental age in the severe patients of 3.5 to 4 years, while the attenuated forms showed a wide spectrum of abilities. They report that the attenuated IIIB patients may have a long period of stability. Twenty three percent of patients had a pattern showing intellectual decline preceding motor regression.

In Spain, the caretakers of 55 patients with MPS III completed a questionnaire about their child's development [149]. Before diagnosis, normal motor development with early mild speech delay, coarse facial features, behavioral problems, and sleep disturbance were reported. Loss of speech around 5 years of age, clumsiness in walking, loss of motor skills with dysphagia, and epilepsy (in half of the patients) were reported in the second or third phase of disease. Psychometric assessment was difficult to evaluate because of variety of tests used; they had no standard protocol. Attenuated patients were not identified but there were a few who retained language and motor skills until very late.

Lin [144] reported from chart review of 28 patients with MPS III, that MPS IIIB was more common in Taiwan. However, initial manifestations were similar to other studies with speech delay and intellectual disability found in all; hirsutism, unstable gait, and hyperactivity in some patients, autism and dysostosis multiplex in one each. Although MRI was done in a subgroup, neurocognitive assessment was not carried out as part of the study; intellectual ability was evaluated from reports in medical records.

Of these 4 studies, only Valstar's study included direct neurocognitive assessment.

4.3.7.2. Longitudinal Studies of MPS IIIA. Buhrman [150] carried out the first longitudinal study using neurocognitive measures (the Mullen Scales of Early Development) in 46 patients with MPS IIIA. Of these patients, only 11 had more than one visit with 35 having only one visit. Severe neurological involvement was accompanied by hearing loss and speech delay, followed by a rapid decline in neurocognitive skills by 3 years of age. Sleep problems began at the age of decline; behavioral problems were also identified early in disease progression. Motor abilities were maintained longer than neurocognitive abilities. Age equivalent scores were plotted to document the patients' decline.

Shapiro et al.'s prospective longitudinal study of MPS IIIA in 24 severely affected children seen over 2 years every six months is presented in three papers [129,151,152]. In the primary paper [129], children were classified by mutation and age of diagnosis into a rapidly progressing ($N = 19$) and slowly progressing ($N = 5$) cohorts. Using the Bayley with the same examiner most of the time, rapidly progressing patients under 28 months continued to acquire skills followed by a slowing of development from 36 to 40 months and loss of skills after 48 months. After 6 years of age, neurocognitive performance reached a nadir of test performance, with a score plateau below an age equivalent of 22 months. Further decline of function was found via telephone interviews in a follow-up report [152]. Adaptive skills had a longer period of acquisition (until 50 months). All these patients had a neurocognitive age equivalent ceiling of 36 months. Thus, no neurocognitive skills developed beyond the mental age equivalent of 36 months. Overall, a mean loss of 15 DQ points over one year was found in children under age 6. This neurocognitive decline was accompanied by significant loss of gray matter using MRI volumetric analysis with a significant correlation between gray matter volume and developmental quotient. Slowly progressing children (two with the S298P mutation and all diagnosed after age 6) were heterogeneous in their clinical progression; some, high functioning enough to be given an instrument above toddler-level: the Kaufman Assessment Battery for Children, Nonverbal Index, showed very slow decline over time compared to the severe group.

Separately, results were reported on the Vineland and subtests of the Bayley of the development of motor skills and speech/language as well as assessment of the usefulness of the Four-Point Scoring System (FPSS) [151]. Compared to language, gross motor skills showed a less steep slope with a fairly stable pattern over time. Parents reported better spontaneous gross motor skills than when elicited in direct examination. This was explained by the patient's lack of the imitation ability needed for direct testing. Receptive language declined more rapidly than expressive language on the Bayley and Vineland, possibly related to hearing loss. The FPSS [124] was found to be insensitive to change in the mid-stages of disease but sensitive in early stages. The FPSS lacked sensitivity when changes were subtle later in the disease, but could be used to monitor treatment outcome in early stage disease.

Finally, a follow-up was done with 14 of the 25 patients from the original study [129] after 3–4 years [152]. Five patients were deceased and all but one slow-progressing patient were functioning below a 2 year level with motor skills slightly more intact. For most, the family burden shifted from behavioral control to physical management of their disease.

A similar prospective longitudinal study was done with MPS III B patients [136]. This was a multicenter study of 19 patients over one year with the same battery of tests as the IIIA study [129]. These patients were older than the patients in the MPS IIIA study, including only two young patients under 42 months. All patients had neurocognitive age equivalent scores of less than two years. The two youngest children showed developmental progress during the study, but the remaining children showed stability at a very low level of functioning. Similarly, MRI volumetric studies mirrored neurocognitive decline with loss of gray matter. A significant difference between the A and B studies, other than the difficulties in recruitment was the heterogeneity of mutations and somewhat reduced predictability in IIIB, compared with IIIA patients.

Truxal [135] carried out a prospective, longitudinal natural history study of 25 patients with 15 IIIA and 10 IIIB patients over one year. The Leiter R and the Mullen Scales of Early Learning were used to measure neurocognitive development. The study suffered from changes in protocol in the middle of the study as the floor on the Leiter was too high, i.e., the test items were too difficult for the patients' level of functioning. Neurocognitive performance in these patients maximized at 2.5 to 3 year old levels with a significant age-related decline with a pattern of decline similar to other studies. Like the combined Shapiro [129] and Whitley [136] studies, there were more MPS IIIA patients under three years of age ($n = 5$) compared to IIIB ($n = 1$) and a similar rate of decline after age 5 years.

Wijberg et al [153] reported preliminary results from a natural history study carried out by Lysogene prior to treatment trials of gene therapy for MPS IIIA. Similar patterns to the Shapiro et al [129] study were found in the neurocognitive and adaptive development of 23 patients, all less than 9 years of age. Some very young children continued adding skills. No child over 5 years of age had a DQ over 50. No child progressed past a 36-month level.

The following meta-analysis includes three prospective studies, while two good studies were not included. The Buhrman study [150] was not included because it was not prospective, and included a preponderance of children ascertained in late stages of disease, which is to be expected when recruitment was done for clinical purposes. The Valstar study was not included because of the wide spectrum of severity with many attenuated patients and the lack of longitudinal follow-up [114].

4.3.7.3. Combined Analysis of Three Prospective Natural History Studies of MPS IIIA. The recent publication of three prospective longitudinal studies of the rapidly progressing form of MPS IIIA (Study 1: Shapiro et al. [129]; Study 2: Wijburg et al. [153]; Study 3: Truxal et al. [135]) provides an opportunity for a combined analysis that helps to define the

range of ages at which neurocognitive development ceases and begins to decline. The rapid progressing form of the MPS IIIA is defined as disease diagnosed before the age of 6 years [132]. This information is crucial for clinical trials to determine the age window that would be most likely to show treatment effects. A combined N of 62 patients were studied over a total of 197 visits.

Each patient was administered either the Bayley Scales of Infant Development-III (Studies 1 and 2) or the Mullen Scales of Early Learning (Study 3). In Fig. 1, all the patients are portrayed using age equivalent scores expressed in months. The dotted lines delineate the traditional cutoff points of neurocognitive ability as standard scores (mean of 100 and standard deviation of 15): normal range (>85), below average/borderline (70–85), mildly impaired (55–70), and moderately impaired (40–55). A limitation to this approach is that these are developmental quotients (DQS) which do not always perfectly align with modern standard scores. DQs are defined as age equivalent score divided by chronological age times 100.

Despite this limitation, these estimates of degrees of impairment may help to identify patients who might benefit in neurocognitive growth from an effective treatment. In this large cohort, only 4 data points of DQ > 85 were found, 8 between 70 and 85, and 23 from 55 to 70. The majority of data points (161/196, or 82%) fall into the range of significant impairment (<55 DQ). While treatment may be directed at other endpoints (e.g., behavior or motor function), significant benefit with treatment in the neurocognitive trajectories of patients below DQ 55 (approximately 3 standard deviations below the mean) seems very unlikely. Fig. 2 shows age equivalent scores by chronological for all three studies.

In Fig. 3, the median scores in 6-month increments were calculated to plot overall developmental trajectories. When means are calculated, the standard deviations were quite large in the scores obtained between 40 and 72 months. Therefore, medians seem to provide a clearer view than means of the pattern of change. Early and late disease are less dispersed; values can be found in Table 5.

Fig. 4 graphs the data from each of the three studies. The findings of Study 1 and Study 3 were more similar, possibly because they were done at one site. Study 2 was a multisite study, which increases variability because of multiple examiners. Although Study 2 patients were more variable, the overlap of these three studies is striking. In all three studies, no child exceeded a mental age of 42 months. Younger children showed growth or stability of neurocognitive skills before 36 months (only from Study 1), but after 7 years no child exceeded 24 months age equivalent score.

4.3.7.4. MPS IIIA Summary. It appears from Figs. 2 and 3 that development continues occurs until 42-47 months (3.5–4 years), plateauing up to 54 months, and falling off rapidly after that. Even while mental development occurs during this time period of life, the mental age equivalents usually do not surpass 36 months. Given the variability, especially from 36 to 78 months (3-6.5 years), prediction for any one patient is difficult. For the group as a whole, however, loss of skills after 54 months is steady, reaching a stable low level of functioning at around 6 years of age.

Such data suggest that further natural history studies of these children using these tools alone are not necessary; parents seeking treatment find natural history studies a burden. Both aspects of this conclusion are consistent with the findings of the updated consensus conference on neuropsychological endpoints [11]. Of course, genotype-phenotype relationships or biomarkers may improve predictability of disease course, but the data collected here certainly seems robust. It also should be pointed out that all but one of the 67 described here

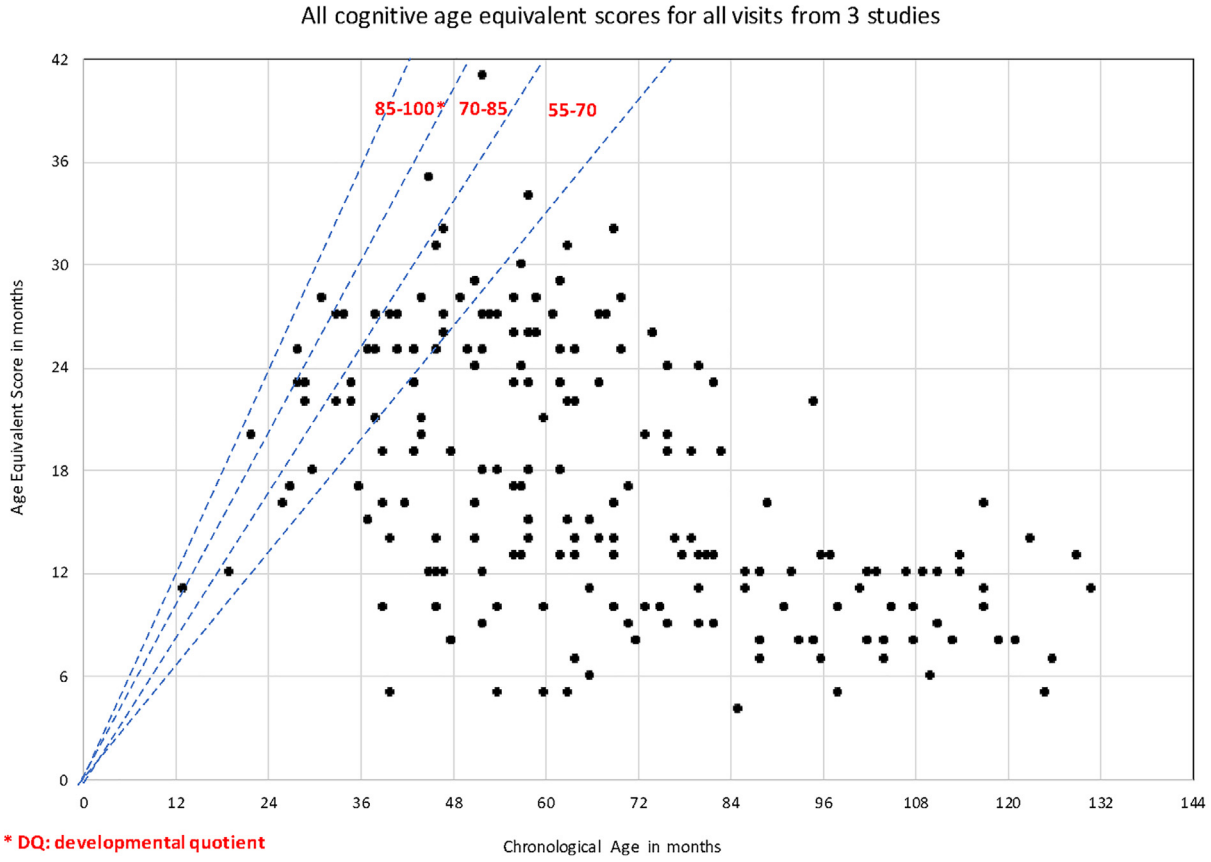

Fig. 2. Age equivalent scores by chronological age from three studies of MPS IIIA.

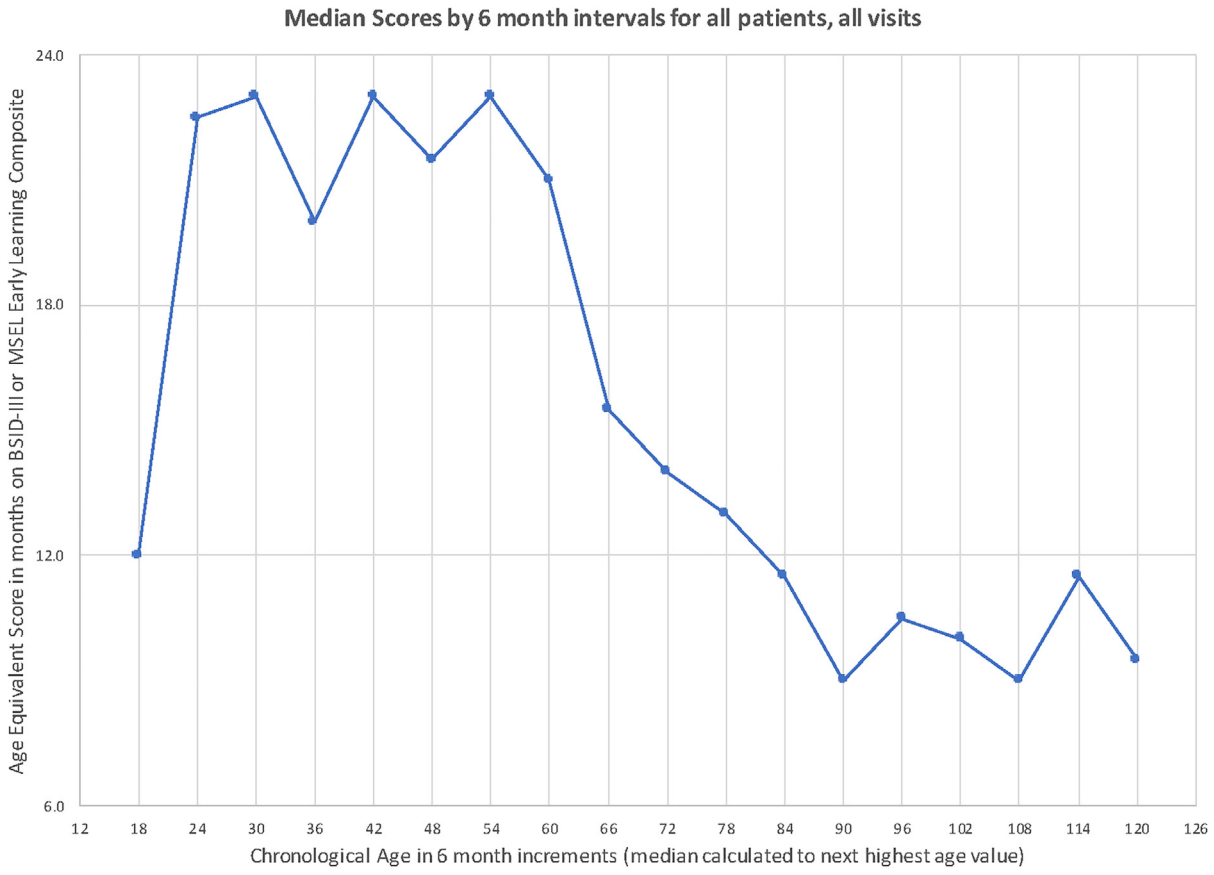

Fig. 3. Median age equivalent Scores by 6 month Intervals of chronological age from three studies of MPS IIIA.

Table 5
Age equivalent scores by 6 month age groups.

Age group	Mean	SD	Median
<24	14.3	4.9	12.0
24–29	21.0	3.6	22.5
30–35	23.9	3.6	23.0
36–41	19.5	7.0	20.0
42–47	22.0	7.2	23.0
48–53	20.2	9.2	21.5
54–59	20.7	7.5	23.0
60–65	18.3	8.0	21.0
66–71	17.9	7.9	15.5
72–77	15.3	6.7	14.0
78–83	15.0	5.1	13.0
84–89	10.3	3.7	11.5
90–95	11.3	5.5	9.0
96–101	9.8	3.3	10.5
102–107	10.1	2.0	10.0
108–113	9.3	2.2	9.0
114–119	11.7	2.7	11.5
>120	9.7	3.6	9.5

were diagnosed before the age of 6 years, which proves to be an effective predictor of the rapid form of MPS IIIA.

While only those children whose trajectories fall above the range of significant impairment in the early stage of the disease are likely to benefit by maintaining or adding skills in neurocognitive ability from new treatments, this does not preclude striving for benefits in other domains.

Combining MPS IIIA data from several studies is necessary to obtain sufficient confidence in the accuracy of the natural history. Sanfilippo A and B are disease that have some variability, but not an excessive amount and slow progressing patients can be reliably separated from those who have a more devastating course with a very short and rapid decline. Although the slowly progressing patients have a lethal disease, albeit somewhat more prolonged, it will be more difficult to demonstrate a treatment effect if they are included in initial clinical trials.

In clinical trials, use of placebo or even non-treated patients who continue to decline rapidly, is not recommended in MPS IIIA (and possibly IIIB). The consistency of the already gathered data, the rarity of finding patients who are young enough to benefit from treatment, and the lethality of the disease suggest that single arm studies with historical comparators is required.

In the meta-analysis both the BSID-III and the Mullen were used. Evidence to support combining data from both tests is presented here. Even though they are not currently recommended, these tests can accurately reflect the downhill course, especially when used in a within-child format; the degree of difference between the Mullen and the Bayley III may be a few points, but the correlation is very high. In 55 administrations of both the BSID-III and the Mullen, in 30 patients (16 IIIA patients and 14 IIIB patients), although the percent differences in BSID and Mullen were greatest in infants under 6 months the overall correlation was 0.94. A Bland Altman plot revealed no differences in distribution (personal communication, Juan Ruiz). It should be noted that the Bayley, while recommended by the Consensus Committee [11,17], has only recently been used in patients with neurodegenerative diseases. The Mullen scales were used for MPS IH pre-and post- HCT at Minnesota until 2014, and historical data using the Mullen is useful as the discrepancies do not exceed the standard errors of measurement for both tests. Note this statement in the Consensus Paper [11] "Of the available tools for evaluating neurocognitive function in this age group, both the Bayley-III (and earlier versions of this measure)

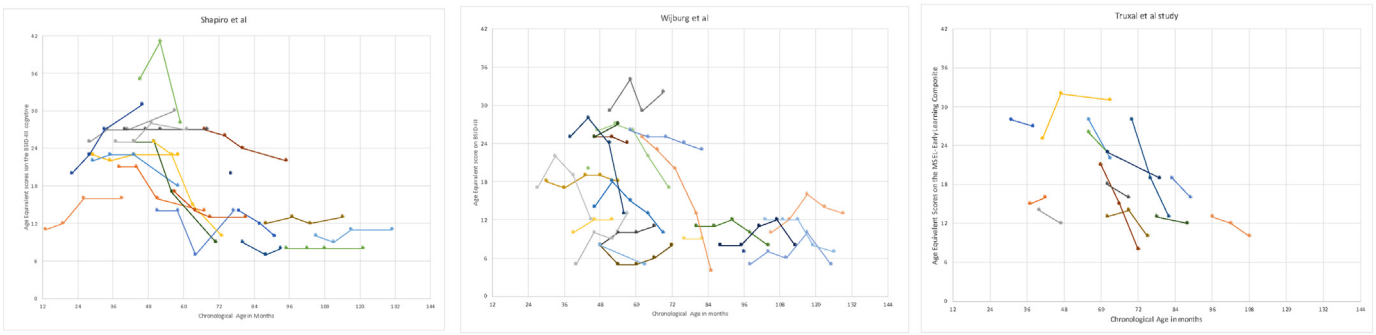

Fig. 4. Individual patient data for each of three studies; age equivalent by chronological age.

and Mullen Scales of Early Learning (MSEL) have been used extensively in clinical studies of mucopolysaccharidoses in the past and both have been shown to be feasible and sensitive to change in patients with these conditions."

4.3.7.5. Summary of MPS IIIB Longitudinal Studies. Three prospective natural history studies with neurocognitive outcomes have been carried out with MPS IIIB. However, data are insufficient to combine the studies to gain a detailed insight into their development. Whitley's multicenter study of 19 patients had only two patients under 42 months [136]. All patients had an age equivalent score of under 24 months, thus they were all quite impaired by the time they entered the study except for the two youngest patients, ages 1.6 and 3.5 years at baseline with DQs of 85 and 62. Both showed neurocognitive growth, but no other patient added skills over the course of the study.

Truxal's study [135] had only 11 patients. All but one were over five years of age at baseline and all had a developmental ages under two years on the Mullen. One patient enrolled at 2.3 years of age and had a Leiter score in the 80s and one Mullen with a score of 18 months at about 28 months; thurs yielding a score somewhat lower than that of the Leiter. The two youngest children added skills, but the remaining children showed stability at a very low level of functioning. Similarly, MRI volumetric studies mirrored neurocognitive decline with loss of gray matter.

A preliminary report from the Biomarin/Allievex natural history study on MPS IIIB patients aged 1-10 years was considered comparative data for their treatment program [154]. All enrolled subjects had deficient NAGLU activity and neurocognitive developmental quotient (DQ) ≥50 at time of enrollment. Cognition and behavior were assessed every 12 weeks and other variables every 24 weeks. CSF heparan sulfate was elevated but not directly correlated with disease status. They reported that neurocognitive decline occurs at a slower rate than in MPS IA. However, that may be due to the selection of slower progressing patients who have a DQ >50. MRI results show that whole brain volume decreases with increased ventricular volume suggesting atrophy. With more details to come in the future, this study may provide important information regarding very young MPS IIIB patients.

A significant difference between the A and B studies, other than the difficulties in recruitment was the heterogeneity of mutations and somewhat reduced predictability in IIIB, compared with IIIA patients. In contrast to MPS IIIA, a complete picture of the natural history is lacking, although most evidence suggests that MPS IIIA and B are similar.

4.3.8. Treatment Studies for MPS IIIA and B

4.3.8.1. Hematopoietic Cell Transplant (HCT). The first treatment tried for MPS III was bone marrow transplant. Vellodi [155] reported the results of bone marrow transplantation for twins with MPS IIIB. Both were engrafted after transplant at 18 months. At baseline DQ scores on the Griffiths Scales of Mental Development were between 80 and 100 and 9 years later between 30 and 40. Neither faced the degree of disability as untreated brothers 9 years after transplant, but they continue to have behavioral abnormality. The question was raised whether this represents any treatment effect or whether it is the normal variability of the developmental trajectory of the disease.

Klein et al. [156]found no benefit of HCT on for a combined MPS IIIA, B, and C sample. 11 patients, successfully engrafted, continued to deteriorate and demonstrate behavioral abnormality. It was concluded that transplant had no benefit, because of limitations due to the older age of the patients, 5 of the 11 being older than 3 years of age.

A report by Kohn et al [157] on a single patient with IIIA who received transplant at age 2.3 years compared to 6 untreated patients with the same mutation (R74C and R245H) found improvement when using the FPSS, the Vineland, and behavioral patterns to track this patient, even though the patient demonstrated global developmental delay.

Welling et al [158]concluded in two patients, one with rapidly progressing IIIA and the other with IIIB attenuated, that considering five years of continued neurocognitive decline and behavioral abnormalities after transplant, no benefit of HCT was evident.

Sivakumur and Wraith [159] found no benefit in neurocognitive development for a 7-month-old sibling over a period of 7 years compared to his untreated sibling.

All of these studies except for that by Kohn cast doubt on the efficacy of HCT.

4.3.8.2. Genistein. Another treatment that has been espoused is the isoflavone genistein, which reduces levels of accumulated heparan sulfate fibroblast cultures of MPS I, II, and III patients [160]. DeRuijter et al [161] enrolled 30 patients in a randomized crossover placebo-controlled study. Although genistein decreased GAGs, neither behavior scores or hair morphology changed. The authors suggest that their lack of findings might be due to a dose that was too small to effect clinical change.

A phase III randomized double blinded placebo controlled clinical trial of high dose genistein was carried out [162] with a partial cross-over of 21 patients (13 IIIA, 4IIIB, and 4 IIIC) whose median ages at baseline ranged from 3.1 to 15.9 years, with a median age of 6.7 years. Standard batteries of neuropsychological tests (Bayley, Vineland, and other measures of behavior, sleep, and quality of life) indicated no change in DQ at 12 months follow-up between genistein and placebo group. It was concluded that genistein is not a viable treatment for MPS III.

4.3.8.3. Intrathecal Enzyme. A trial conducted by Shire (now Takeda) [163] enrolled 21 patients between 12 and 48 months randomized to a 2 week, 4, week or no treatment schedule using intrathecal administration of recombinant enzyme. Outcome was assessed by Bayley

developmental quotient and age equivalent scores as well as by cortical gray matter volume, Vineland, and urinary/CSF GAGs. Three patients treated showed benefit which did not meet the goals of study, but which did reduce GAGs. Responders were the youngest or highest functioning patients. The study was discontinued as the treatment did not attain set goals. Lack of response may have been due to the baseline age and developmental levels of the participants, or lack of efficacy of the treatment.

4.3.8.4. Ongoing Trials. Currently five gene therapy trials and one enzyme replacement trial, (all using the recommended Bayley and Vineland scales to measure outcome) are active with some preliminary results. An initial trial [164] of the intracerebral administration of AAVrh.10 vector carrying the gene for the human SGSH enzyme was safe and well tolerated after one year in the four children studied, validating the surgical approach for direct AAV vector delivery in the brain parenchyma. Neurocognitive evaluations suggested a neurocognitive benefit in the youngest child receiving the vector. Following this initial trial, Lysogene is currently conducting an open label clinical trial of 20 children to be followed for two years; however, it is on hold because of localized findings on MRI images at intracerebral injection sites.

Interim results [165] showed that IV administration of an AAV-9 vector (Abeona) expressing the SGSH gene in 14 children with MPS IIIA from 11.5 to 26.5 months was safe with no adverse effects. Follow-up of up to 18 months indicated several patients with neurocognitive stabilization. For 6 children with MPS IIIB, treatment was safe and activity of the NAGLU gene was found in the liver and CNS [166].

Interim results of ICV administered enzyme replacement therapy to patients with Sanfilippo type B in Part 1 of the study (Allievex/Biomarin) demonstrates decrease of HS in CSF to normal levels in 3 patients as well as improvement in DQ in 2 of 3. Patients will continue on to Part 2 of the study [167].

The University of Manchester (together with Orchard Therapeutics) have started recruiting for a Phase I-II ex vivo lentiviral vector trial for MPS IIIA (Clinicaltrials.gov).

Given the failure of early initial attempts at therapy with HCT, genistein, and intrathecal enzyme replacement and the serious unmet need in this disease, one may be optimistic that these trials will provide some hope for these patients.

4.3.9. Sanfilippo Type C

Sanfilippo type C is a rarer subtype than types A or B. Abnormal function of the enzyme heparan-alpha-glucosaminide N-acetyltransferase (HGSNAT) is associated with a broad spectrum of mutation types [168]. It can be associated with missense mutations causing complete loss of detectable enzyme activity [169]. Studies report onset of clinical symptoms at variable ages with variable severity and rates of regression. Ruijter et al. [170] carried out a natural history study and found a milder but more variable course than with the other types especially in verbal and motor functions. In this study, speech decline preceded that of motor decline. Note that this is the case also for documented regression in patients with MPS IIIA and B.

Case reports include both very early onset (1–2 years of age) [171] and later onset (3 to 7 years of age) [169,172–176]. Fedele et al. [177] reported both early and later onsets in their series. This variation may reflect both disease factors and how onset is defined. As in other forms, clinical symptoms include severe deterioration in childhood, with hyperactivity, sleep disorders, behavioral problems, hearing loss and neurocognitive decline [169]. Many studies report consanguinity in families of type C children [171,174,175,177].

Thus far, no prospective natural history study has been carried out with quantitative measures of cognition, as is necessary for treatment trials. Gene therapy is also being investigated as a treatment for Sanflippo type C.

4.3.10. Sanfilippo Type D

This is the rarest form of Sanfilippo syndrome is caused by a deficiency of N-Acetylglucosamine-6-sulfate sulfatase. Initial reports of 4 cases in the Italian literature were characterized by phenotypic heterogeneity with both mild and severe manifestations [178,179]. Since then a patient with a language disorder (verbal auditory agnosia) was described without physical features of MPS [180]. It should be noted that verbal auditory agnosia was also clinically described in a natural history study of MPS IIIA [9]. Jones et al. [181] described two patients, one with slow overall development followed by loss of skills at 7 and the other with decline after age 2.5. The description of one child (but with no testing) indicated mental impairment, but the other was too young to describe a clinical course. Both had Italian ancestry [182]. Beesley [183] reports a Pakistani boy with a relatively intact cognition by clinical report but difficulty with verbal understanding. Different from these cases, Siciliano et al [184] reports two sisters; the first lost skills at four years of age with aggressive behavior but continued ability in motor function at age 19; her sister was less delayed and began to show regression at age 11 years. Thus, heterogeneity of onset and rate of progression may, as in type C, be characteristic.

Valstar et al [185] described clinical signs and symptoms of 12 MPS IIID patients who appeared to be similar to previously described patients with other forms of MPS III. Early development was normal with onset of behavioral problems around the age of 4 years, followed by developmental plateau, decline of verbal communication and subsequent deterioration of motor functions. Overview of the 31 patients in the literature suggested that, while there is a preponderance of Italian patients, no founder mutation could be identified [182]. In this overview, onset appears to be somewhat later than in other MPS III types, with many around 4 years of age, but diagnosis did not occur for many until much later (range from 4 to 16). Speech problems were found to be a major issue as well as behavior. Similar to type C, no prospective natural history study has been carried out with quantitative measures. Gene therapy and enzyme replacement are also being investigated for type D.

4.3.11. The Status of Natural History Studies in MPS III; Where Do We Go From Here?

The number of patients available for natural history studies is rapidly diminishing in this rare disease as parents opt to enroll in studies that offer any hope to stabilize or normalize development. Thus far, prospective natural history studies in both IIIA and IIIB have illuminated the devastating course of this disease with onset in the first two years of life, halting of development by 36 months, and loss of skills starting around 40–48 months of age [129,135,136,154]. There are several important studies being done currently with initial results indicating that unless intervention occurs very early, before damage to the neural substrate is irreparable, treatment effects cannot be demonstrated. This creates a no-win situation where in order for newborn screening to occur to be able to treat all children, a treatment effect must be shown. A clinical treatment effect likely cannot be shown in children who are over 3 at recruitment, making it impossible to obtain likely 0responders to treatment. Furthermore, no early diagnosed patient's parents will knowingly participate in a study in which they would have to wait for treatment, passing the stage where response is feasible, and the inevitable outcome is dementia and death for the child. The only solution here is to use data from a combined analysis of all studies using known measures of developmental trajectories that can provide the needed comparator group for companies seeking to demonstrate that their treatment has a clinical effect. Use of placebo or even non-treated patients who continue to decline rapidly, is not recommended in MPS IIIA (and possibly IIIB). Single arm studies with historical comparators may provide the only method of demonstrating efficacy in young patients with a lethal disease.

4.4. MPS IV

Mucopolysaccharidosis type IVA (Morquio syndrome) is caused by deficiency in N-acetylgalactosamine-6- sulfate sulfatase (GALNS) and is associated with abnormal deposition in cells of keratan sulfate and chondroitin-6 sulfate [186]. Extremely rare even among MPS types, MPS IVB syndrome is clinically indistinguishable from IVA, but is caused by abnormalities of the GLB1 gene and decreased activity of ß-galactosidase with similar keratan sulfate accumulation. Some of the studies below combine the two forms of MPS IV.

In the literature, patients with MPS IV have been described as being without neurocognitive or behavioral impairment; particularly as the disease lacks involvement of heparan sulfate and dermatan sulfate, common in the MPS disorders associated with neurocognitive decline [187] MPS IV is described primarily as a visceral and skeletal disorder, with short stature, impaired endurance, hearing problems, respiratory problems, and cervical spine instability. It is widely believed neurocognitive difficulties are not present [186,188,189], even though anxiety and depression may be present [190]. These commonly held opinions may be due to the lack of investigation into cognition and behavior, and differing opinions about what constitutes neurocognitive and behavioral impairment [191]. There is some emerging evidence to the contrary, described below.

4.4.1. Clinical Presentation

Symptoms begin after the first year of life with a mean age of diagnosis of 4 to 5 years with progressive skeletal dysplasia. Anxiety and depression may also be present [187]. Physical mobility is altered in MPS IV: major skeletal abnormalities, short stature, and limited respiratory function result in poor endurance, increasing functional limitations and reducing quality of life over time [95,192,193]. Pain is a common complaint and interferes with quality of life [194]. Of the MPS disorders, pain is most severe in MPS IV [195] but no specific studies could be found on the effect of pain in MPS IV on neurocognitive or behavioral functions. Hearing problems are also prevalent, both conductive and sensory neural [196], worsening with age and associated with height, a proxy for skeletal dysplasia. However, early speech and language developmental problems were not reported by parents or patients.

Severity of the disease is related to age of onset with a severe form being diagnosed in the first year of life, a moderate form between one and five, and an attenuated form diagnosed after age five [188]. Both age of onset and progression are variable [189]. Severity is also related to life span with survival ranging from the third decade to a normal life span [189]. On a scale of Activities of Daily Living (ADL), Yasuda and colleagues found that scores decreased with age, and that severe patients scored lower than attenuated patients [197].

ERT is a treatment option for MPS IV; the six-minute-walk test demonstrates significant improvement with ERT but does not decrease the need for surgeries [198]. Hematopoietic cell transplant is also an option, but only a few case reports have been published [199,200]. In four patients with MPS IV, three severe and one attenuated, improvement after HCT was seen in activities of daily living, respiratory function, and biochemical findings; further, and none needed a wheelchair [200].

In an MRI study of 11 MPS IV patients, all had spinal degenerative disease with a risk of cord compression. With respect to overall effects on the CNS, one patient had neurocognitive impairment, and two others had nonspecific white matter changes. In two other patients, enlargements of the subarachnoid spaces were found [201]. Davison and colleagues also found in 8 children who had neurocognitive assessment that 3 had normal MRIs, and the rest had various white matter abnormalities. No association was found between IQ and MRI abnormalities [191]. Zafeiriou and Batzios [3] found that white matter abnormalities, while present on MRI, are not as frequent as in other MPS disorders.

4.4.2. Neurocognitive and Behavioral Studies

A handful of studies have addressed neurocognitive and behavioral abnormalities in MPS IV, but no study has addressed the natural history of these domains. One study by Davison et al. [191] used age-appropriate neurocognitive measures and the Child Behavior Checklist in nine children. Four scored below average and 2 of these fell into the cognitively impaired range on the Wechsler Full Scale IQ (General Ability Index). Another child could not be administered the neurocognitive test, but the Vineland indicated below average functioning. It should be noted that 5 of 9 children functioning below the average range is beyond expectations (In typically developing populations 16% would fall into the below average range of less than 85; in this sample we have 56%). Eight of 9 children were described as “can’t sit still or concentrate” Six of the 9 children were described as “talks too much.” In addition, difficulties in attention/concentration were apparent. In three patients an association was found between N-acetyl aspartate concentration (a measure of neuronal integrity) by magnetic resonance spectroscopy and the neurocognitive indices. The authors suggest that the issues may be in calcium trafficking and resultant amygdala abnormality, as in Williams syndrome [191].

In a sophisticated laboratory study, Blundell et al. [202] using measures of attention, language, visual processing efficiency, and ocular-motor function compared children with MPS IVA with those with Tyrosemia. Patients with MPS IVA showed significant difficulty with visual search and maintaining gaze. Sustained attention was felt to be the underlying impairment with deficits in the amount of fixation time after the onset of the stimulus. Search times were delayed and were not consistent with ‘occasional’ lapses of attention. While the underlying brain mechanism of the problem is not clear, the authors hypothesized that neuroaxonal connection formation is affected by keratan sulfate and chondroitin-6-sulfate, and that calcium signaling may also be disrupted. They observed that the problems with fixation times may explain the parent-reported difficulties with sustained attention in the Davison et al. [191] study. They noted that a number of widely distributed brain areas are known to be implicated in maintaining fixation [202].

Spurlock et al. [203]in a poster presentation, reported a comprehensive neuropsychological assessment of 11 patients with MPS IV, 6 below 18 and 5 above 18 years of age, using the CANTAB (Cambridge Neuropsychological Test Automated Battery). Results indicated normal cognition, memory, and visual spatial abilities, but below average attentional skills using the T.O.V.A. (Test of Variables of Attention), including consistency of focus in both the younger and older groups, and vigilance in the younger group.

Ibanez & Barreto [95]found no problems in cognition, but difficulties in fine motor activity and visual tracking in six MPS IVA patients who had a median age of 9 years. Visual attention appears to be an area of weakness detected by the NAC (Neuropsychological Assessment of Children), a neuropsychological measure in Spanish.

Taken together, these studies suggest that while a few children with MPS IV have overall intellectual impairment, more patients may have difficulties with executive functions such as attention and processing efficiency, especially in the visual domain. This may have influenced neurocognitive ability scores in the Davison et al study [191]. What does this mean with regard to causation? Executive function depends on wide ranging brain functions, likely based on broad connectivity across the brain subserved by white matter connections. Consistent with this hypothesis, abnormalities of white matter are frequent findings in all MPS disorders, including MPS IV [3,191,201].

One study has addressed psychological functioning, quality of life and pain severity in MPS IV. Ali et al [204] administered measures of these variables to 20 adults with MPS IVA. 55% had scores in the symptomatic range on the measure of psychological functioning ASEBA Adult Self Report (ASR). These patients, in turn, had higher pain severity and pain interference scores. Interestingly, the Intrusive scale on the ASR

was the most frequently elevated scale (30% or 6 of 20 were in the clinical range), including items relating to behavior such as "*Brags, Loud, Shows off, Talks too much, Teases a lot,* and *Tries to get a lot of attention.*" QOL as measured on the SF 36 did not differ between those with symptomatic scores on the ASR and those without. No measure of disease severity was included in this study. It is interesting to consider the similarity of the description of intrusive behavior in this study and the description in Davison's study [191]of "talks too much." Research is needed to quantify this behavior and to determine if it is related to executive dysfunction as well as the causative neural substrate.

4.4.3. Summary and Needs

An important factor to consider in future studies is the alteration of life experience for those with mobility problems, hearing loss, and pain. No studies have addressed these issues in detail or with a sufficient number of patients. There are no longitudinal studies of cognition, nor any studies of the relationship of quantitative measures of brain structure and function to cognition and behavioral manifestations. Although depression and anxiety are mentioned [190,198], neither these problems nor the hypersocial behavior noted in two reports [191,204] have been studied in relation to somatic and brain abnormalities.

4.5. MPS VI

MPS VI, also known as Maroteaux Lamy syndrome, is caused by a deficiency of N-acetylglucosamine-4- sulfatase, also known as arylsulfatase B (ARSB), which leads to dermatan sulfate and chondroitin sulfate storage, which are in turn associated with diverse clinical manifestations [205–208]. MPS VI is very rare, with an incidence that ranges with country/ethnic group ranging from.36 to 1.3/100,000 births [205].

4.5.1. Clinical Symptoms

Somatic symptoms vary but short stature, facial coarsening, skeletal abnormalities, hearing loss, cardiac involvement, corneal clouding, carpal tunnel syndrome, and spinal cord compression are common symptoms [205,209,210]. The literature indicates no neurocognitive abnormalities [208,210,211], but studies have not been detailed. A rapidly progressive form of the disease is associated with a rapid onset of clinical manifestations, notably severe musculoskeletal disease, usually before the age of 2 years. Without treatment life expectancy for these rapidly progressing patients is less than 20 years [205]. The slowly progressing phenotype has normal or only mildly coarsened facial features, a slightly reduced to normal body height, and less prominent skeletal dysplasia compared to the rapidly progressing phenotype. Eventually, however, these patients also develop skeletal symptoms, reduced endurance, and need for multiple surgeries [205]. Most MPS VI patients have poor quality of life due to frequent surgeries, sensory impairments, poor mobility, and functional disability [205,212].

Azevado's study of 28 South American patients found the mean age at diagnoses was 48.4 months [210] and 88% had symptoms before age 36 months by history. The number of clinical manifestations were not correlated with urinary GAGs or ARSB levels. A large number of cardiac manifestations were found. A survey of 121 patients over 4 years of age at 7 centers with MPS VI [212] found that, urinary GAG levels predict clinical parameters including endurance as measured by the 6-minute-walk test (6 MWT). Furthermore, these patients almost universally had impaired performance, short stature, cardiac abnormalities, low lung volumes, and impaired shoulder flexion. CHAQ/HAQ scores (a measure of disability) in younger patients were relatively more impaired, due to more rapidly advancing disease.

A 12-year follow-up of 117 of the patients in the previous study included medical histories and clinical assessments (n=59) and survival analysis (n = 117) [213]. All patients were on ERT treatment in the interim. All patients increased in height, showed improvement in respiratory tests and endurance (6 MWT) and improved survival. Many of these patients still required surgeries and other clinical interventions for spinal cord decompression, heart valve replacements, hip replacements, and corneal transplants. No changes were seen in the moderate level disability scores on the CHAQ/HAQ. Pain levels were mild at baseline and follow-up.

4.5.2. Genotype/Phenotype Analysis

Because of the large number of novel and private mutations, phenotype-genotype correlations are difficult in MPS VI, and do not readily separate severe from mild clinical presentations. A few mutations can be definitely be associated with severe disease such as the L321P mutation associated with early onset [209]and the Y251X mutation which has been found to cause severe disease in 18 Saudi Arabian patients in 6 families [214]. An informative graphical presentation of disease-causing mutations is shown on the ARSB gene coded for severity [205,212]. The authors showed that, in addition to nonsense mutations and deletions, that a number of missense mutations appear to be associated with severe disease.

4.5.3. Neurocognitive and Neurobehavioral Studies

Although the rate of progression of somatic disease and its relationship to mutation type have been described [205], no studies have addressed neurocognitive status. Much is known about the somatic signs and symptoms, but the roles of brain abnormality and neurocognitive function in MPS VI have not been well studied [215].

Throughout the literature it is stated that neurocognitive ability in MPS VI is preserved [205,213,216] but with little documentation using neurocognitive testing. Consistent with this view, decreased hearing and vision, physical disabilities, and cultural deprivation have been a rationale to explain the finding that a significant proportion of patients with MPS VI can be classified as below average or cognitively impaired [213,217].

Despite this view that cognition is normal, brain abnormalities such as white matter lesions and perivascular spaces, communicating hydrocephalus and ventricular enlargement have been described in patients with MPS VI [2,3,217–219]. Brain abnormalities in MPS VI, mainly white matter abnormalities, have not been found to be strongly associated with poor intellectual development.

In a recent study by Azevedo et al. [217], MRI and neurocognitive testing were performed on 25 MPS VI patients with a mean age of 10.6 years. Five of these patients had an IQ below the normal range (69 or lower). Brain abnormalities as measured by presence of lesions, white matter lesion load, and cerebral volume were present in 19 of 21 patients but were not correlated with IQ scores or urinary GAGs. This is similar to findings in attenuated MPS I [44]. The investigators [217]suggested that cultural deprivation and physical limitations associated with the disease (fatigue, and visual or hearing deficits) may have an impact on the outcome of IQ testing in these patients. To support this, they also performed an analysis examining the "Cognitive Potential" of their patients. This adaptation of the Wechsler tests for Portuguese children and adults averaged scale scores based only on the tests that the patients were able to complete. Using standard total IQ score of the 16 children who were able to complete the whole test, 31.2% fell in the cognitively impaired range. Using their adapted 'Cognitive Potential' measure for the entire 25 patients, 16% were cognitively impaired. They excluded the visual and hearing impaired, dropping the percentage to 8.7%. Even at this latter number, only 2% of the normal population fall into the cognitively impaired range, providing evidence that there is likely a substantial subset of MPS VI patients who are cognitively impaired due to disease. Thus, despite their analysis evidence for neurocognitive impairment in some patients is present in MPS VI.

Ahmed [54] studied attenuated MPS I and II and MPS VI. She found that there was a negative association of the PSS score (Physical Symptoms Score) with IQ and attention in MPS VI, concluding that the association reflects disease severity in both the somatic and neuropsychological domains.

Another study [220] examined functioning independence using the PEDI (Pediatric Evaluation of Disability Inventory) and the FIM (Functional Independence Measure) in 24 MPS VI patients from 2-18 years. They found a 33% decrease in the PEDI compared to a normal control and they concluded that functional capacity was significantly reduced in children with MPS VI, even though the report states that cognition is normal. However, no measurement of cognition was performed.

4.5.4. Natural History Studies

Ebbink [215]carried out the only natural history study of cognition thus far in MPS VI. She studied 11 children ages 2 to 20 using the Bayley, the Griffiths, and the Wechsler Scales. A parent or sibling was also tested for comparative purposes. MRIs and genotypes were also collected. Four of 11 were found to have a rapid progressing somatic disease with onset between ages 4 and 7. The patients IQ scores ranged from normal to mentally delayed with long term stability. The mutation Y210C was associated with higher IQ levels. Two patients with severe genotypes did worse. She concluded that neurocognitive abnormalities were produced by disease as well as by environmental factors.

4.5.5. Treatment

The first treatment to be developed for MPS VI was HCT. A bone marrow transplant was done on a cognitively normal functioning young woman with MPS VI in 1982 with good results [221]. Until the development of ERT, HCT was the only treatment available. Studies of long-term outcomes of HCT treatment of MPS VI have found mortality rates similar to those of MPS I; however, most transplants were done a long time ago as few patients opt for this treatment with the current availability of recombinant enzyme. A review [222]suggests that patients with MPS VI benefit from HCT and that the overall clinical condition improves, although cognition was not explored in relationship to improvement. Facial dysmorphism, hepatosplenomegaly joint mobility and cardiac symptoms were found to improve [221,223,224].

The only study that could be found comparing the cognition in MPS VI patients who had ERT and HCT was a study of 12 patients, ages 13 to 22 years, 7 with ERT, and 5 with HCT, one of whom was unengrafted and who subsequently was on ERT [225]. In the 4 with HCT all had average IQ, adaptive skills, reaction time and attention span. 7 patients with ERT had average IQ, average adaptive skills, average reaction time, but below average attention span. All 12 patients had poor visual motor skills, likely due to peripheral rather than central disease.

Patients on ERT are followed on the MPS VI Clinical Surveillance Program but neurocognitive data is not collected. However, registry data suggests that ERT treatment results in better growth and improvements in endurance, hepatosplenomegaly, and pulmonary function [226]. Long term follow-up of ERT suggests that improvements in endurance in turn result in improved activities of daily living [227]. However, despite ERT treatment, a study employing focus groups with 9 patients and caregivers, suggested that limited mobility, decreased range of motion, pain and fatigue restricted social interactions and engagement in home, community and educational environments [228].

4.5.6. Summary of MPS VI

Neurocognitive ability in patients with MPS VI has not been extensively studied. The incidence of cognitive impairment is not known, but in both Azevedo's study [217] and Ebbink's study [215], about 28-30% tested in the impaired range; however, Azevedo makes the case that this is an overestimate. The lack of data regarding the incidence of cognitive impairment in MPS VI is a major deficiency in the literature. Despite the belief that they are cognitively normal, some patients were found to have neurocognitive limitations in these exploratory studies, and a proportion have documented attention difficulties. Because the scope of assessment was limited to IQ, attention problems and other undocumented neuropsychological limitations have not been carefully explored.

Furthermore, the finding of association of attention with white matter abnormalities in other MPS disorders, would suggest that MRI studies of associations with attention/processing functions may be a fruitful area of further research. Attention problems may contribute to poorer quality of life, which for these patients is already decreased due to limited mobility, pain, and fatigue. Detailed examination of disability associated with attention and psychological status is recommended.

4.6. MPS VII

MPS VII (Sly syndrome) is extremely rare among MPS diseases, with a reported global incidence of less than 200 patients [229,230]. It is an autosomal recessive disorder produced by deficiency of ß-glucuronidase (GUSB) [231]. Due to this deficiency, chondroitin sulfate (CS), dermatan sulfate (DS), and heparan sulfate (HS) are insufficiently degraded and accumulate in the lysosomes of many tissues, leading to cellular and organ dysfunction [232].

4.6.1. Clinical Phenotypes

Phenotypes vary from severe forms with skeletal dysplasia and neurocognitive decline to attenuated forms with mild symptoms. A survey of physicians [233] on 56 patients from 11 counties found short stature, skeletal dysplasia, hepatosplenomegaly, hernias, cardiac involvement, pulmonary insufficiency, and neurocognitive impairment.

MPS VII is unique and differs from MPS I and II by having a high incidence of neonatal nonimmune hydrops fetalis (NIHF). NIHF characteristically shows marked ascites (accumulation of fluid in the peritoneal cavity causing abdominal swelling), edema of the limbs, hepatosplenomegaly, delayed brain development, mild decrease of ventricular function, liver disease, severe lung hypoplasia dilated heart and, at autopsy, presence of foamy macrophages in the brain.

The survey referenced above [233] found that 10 of the 56 patients had prenatal-onset NIHF. Of those with prenatal-onset hydrops that survived gestation, most died in early infancy of heart, kidney or respiratory failure. 13 patients had the infantile or adolescent form with history of NIHF and showed a wide range of phenotypes. Presence of NIHF does not necessarily predict the subsequent severity of the disease if the child survives infancy. 33 patients had the childhood/adolescent form with no NIHF with a wide range of disease severity. However, no study has actually systematically examined the neurocognitive outcomes of these children.

There are indications that onset of MPS VII is quite variable. Unlike with other MPS disorders, MPS VII patients frequently are symptomatic at birth, suggesting a prenatal onset [234] although there is considerable diagnostic delay even in patients without NIHF. 7 patients without NIHF had a median age of 6 years at diagnosis suggesting significant delay [235].

Neurologic signs such as cord compression, with associated hyperreflexia and clonus were found in 28% of patients by Moñtana et al [233] Symptoms of language delay (94%) and intellectual disability (86%) were prevalent by report, but longitudinal data were absent. Presumably, like MPS I and II, there is a gradual decline over time in neurocognitive function; however, the timing is unknown. There are reported cases of relatively normal neurocognitive function, but most patients appear to have some degree of impairment. No longitudinal natural history studies have been carried out.

4.6.2. Genotype/Phenotype Correlation

49 different mutations have been reported [232] with classification of attenuated or severe by 1) clinical judgment of the phenotype of patients homozygous for a mutation, 2) in vitro expression, 3) prediction of likely change in protein structure, and 4) presence of a dominant second allele permitting residual enzyme activity. In all 15 mutations were associated with a severe phenotype and 14 with an attenuated phenotype. One had a normal phenotype (pseudodeficiency allele). Nonsense mutations and deletions were mostly associated with severe

phenotypes [232]. In a family reported from Brazil [236], despite a mutation that had been previously reported as attenuated, variable phenotypes were seen in this family ranging from severe to moderate.

4.6.3. Treatment

BMT has been used for a few patients with MPS VII with variable success. A 12 year old Japanese girl had a successful BMT [237]. Clinical improvement was dramatic, especially in motor and upper respiratory tract functions. However, she had an IQ of 50 (the floor of the test) on the WISC-R with no change after BMT. 17- and 22-year follow-ups on the Tanaka-Binet V were at 37, a 6 year old level at both visits, suggesting stability of neurocognitive function. However, several skeletal changes were observed as well as decline in hearing [238] though she was still mobile. Another 2-year-old girl had HCT twice (due to failure of engraftment on the first try) [239]. The goal was to stabilize skeletal problems and prevent neurocognitive change. The patient was reported to have normal daily activities for her age and skeletal dysplasia had stabilized. She had a follow-up at age 9 with an average IQ. It was not determined whether this patient might have an attenuated phenotype. Furlan et al [240] reported a patient with NIHF, diagnosed during his mother's pregnancy, who had dysmorphic features at birth. At 14 months, after many infections and surgeries, he underwent successful HCT. However, his respiratory problems worsened and he died of an RSV infection at 25 months.

Beneficial enzyme replacement therapy outcomes were reported in several studies [241–244] Enzyme replacement with vestronidase alfa was approved in November 2017 by the FDA and in 2018 by the EMA based on a study of 12 patients using what Harmatz et al [230] called a 'randomized, placebo-controlled Blind-start' design. Criteria for response included prespecified minimally important differences including uGAGs, 6MWT, FVC, shoulder flexion, visual acuity, and the BOT (Bruininks Oseretsky Test of Motor Proficiency). In addition, investigators examined fatigue on the PedsQL. A long-term extension study confirmed these results [243].

4.6.4. Natural History of Neurocognitive Function

A rigorous disease monitoring program, post-approval, of vestronidase alfa was developed by Ultragenx [229]. In order to test neurocognitive and adaptive functions, MPS VII patients will be seen in academic centers, with presumably trained assessors. The Vineland and age-appropriate neurocognitive assessment will be carried out along with the 6 MWT, QOL, and disability measures, and clinical somatic measures. Note that this will provide the first prospective longitudinal neurocognitive data for MPS VII. Vestronidase alfa is not expected to cross the blood-brain barrier, thus there may be no direct benefits to cognition or general neurological effects [245]. Cognition may nonetheless benefit from improved somatic status in motor, hearing, and physical well-being. The data from this program should therefore provide optimal comparative data for future brain treatment.

4.6.5. Summary and Needs

Very little data exist on neurocognitive and behavioral function in MPS VII. Prospective, longitudinal direct measurement data are needed to describe the neurocognitive developmental course and the effect of NIHF on neurocognitive and behavioral development. Following that, treatment of brain disease can be measured on those tests that are sensitive to disease effects. ERT will be the standard of care so that neurocognitive and behavioral data will be gathered in that context. Presumably once such data are collected, movement toward brain treatment can proceed.

5. Conclusions

While considerable progress has been made in understanding the neurocognitive difficulties of patients with the mucopolysaccharide disorders, their neurocognitive natural history and predictors of neurocognitive outcomes, much is left to do (See Table 6 for summary). Clinical trials depend on this information. In brain disorders, the treatment effects must be pervasive and persistent.

MPS IH is the only type that has a treatment that halts the progress of the CNS disease, and HCT has become the standard of care. However, because the risk from HCT is greater than desirable and the results imperfect, better treatments must be designed and are in development. New treatments must be comparable to or better than HCT and must be applicable in the youngest children. While MPS I demonstrates a spectrum of severity and brain involvement.

The data indicate that many patients with MPS IA have neurocognitive abnormalities, although stable or minimally

Table 6
Summary of needs for studies of neurocognition by MPS type.

MPS type	Needs
MPS IH	• Because most patients are currently treated with HCT, studies documenting natural history are not needed, and outcomes of standard of care are not as important unless they provide novel information related to predictors of functional outcomes. • Studies of effects of novel therapies to address residual intellectual, attention and processing deficits using HCT outcomes as a comparator. • Studies characterizing development of patients identified by newborn screening.
MPS IA	• Longitudinal prospective studies to address attention, executive function, and cognition with covariates of somatic severity, and genotype. Length of time on current standard of care may also affect outcome.
MPS II, all phenotypes	• Longitudinal, prospective studies to improve the prediction of the neurocognitive developmental trajectory including somatic severity, genotypes, and biomarkers. Such studies necessarily need to address the interaction of behavioral abnormality with neurocognitive profile.
MPS II, non-neuronopathic	• Studies of attention and executive function with quantitative MRI to better understand neural basis of neurocognitive abnormalities with consideration of somatic severity, genotype, and length of time on ERT therapy.
MPS IIIA and B	• Combining current natural history data to provide robust comparator data to obviate future natural history studies. This is necessary to provide historical comparators for single armed studies in young patients with a lethal disease. • Further studies of slower progressing and attenuated patients of their natural history of neurocognitive and behavioral abnormality.
MPS IIIC and D	• International studies (longitudinal or cross-sectional, prospective or retrospective) of cognition and behavior considering somatic symptoms and genotype.
MPS IVA	• Both cross sectional and longitudinal studies of neurocognition including IQ, attention, executive function, and behavior (emotional, social) together with neuroimaging studies to clarify brain behavior associations. • Consideration of the effects of somatic symptoms, mobility, hearing loss, and pain on neurocognition and behavior are crucial.
MPS IVB	• Initial retrospective studies of patients with directly quantified neurocognitive function. Due to the rarity, prospective studies may be difficult to accomplish.
MPS VI	• Longitudinal, prospective studies to improve the prediction of the patient's neurocognitive developmental trajectory as well as other neuropsychological functions such as attention, executive function, processing speed, and memory together with imaging. • Consideration of the contribution of somatic severity, mobility, genotypes, and biomarkers will be critical.
MPS VII	• International longitudinal prospective or retrospective to describe the neurocognitive and behavioral developmental course as well as the effect of NIHF on outcomes. The disease monitoring program that is currently ongoing will contribute initial data to that effort.

progressive over time. Below average cognition, present in MPS I, has not been the focus of studies, yet quality of life depends in part on educational and life success which are associated with neurocognitive ability. Pursuing neurocognitive assessment of attenuated patients to understand their neurocognitive profiles in the clinic and developing treatment that can benefit brain function are necessary next steps. Because MPS I has been found in large part to be a white matter disease which affects attention and executive function, possibilities for effective treatment may be better than for those conditions in which there is neuronal loss.

The great variability of MPS II makes it difficult to study its natural history. No clear criteria separate the neuronopathic patients who decline and those who have a long period of stable low functioning. Recent studies suggest that mutation type may help to classify those who might decline earlier. The pressing need for treatment of this multisymptomatic disease, with its somatic, neurocognitive, and behavioral abnormalities, has made it difficult to carry out extensive natural history studies, especially those necessarily lengthy studies on stable neuronopathic patients. MPS II patients have a wide spectrum of neurocognitive abilities, but even those who are attenuated, as in MPS I, suffer from attention and executive function deficiencies, probably due to white matter abnormalities, which need further study and treatment, given emerging evidence to support longstanding patient reports of the impact on quality of life. More than any other of the MPS disorders, because of its all-encompassing presentation, a multi-pronged approach to a long-term natural history of MPS II, with mutation analysis, imaging, cognition, behavior, disability, and assessment of somatic abnormalities including motor function and hearing, is needed. Carrying out and funding such a project would be a challenge, and perhaps it is too late.

MPS III (particularly IIIA), unlike the other MPS disorders, has had many studies of natural history. This is probably due to the lack of any effective treatment for this neurodegenerative disease. For the under-5-year-old, rapid progressing patients, neurocognitive natural histories had consistent findings in the three studies that were presented here. Inclusion of the more slowly progressive forms in clinical trials would likely confound any treatment results. Although very similar in the early years of the disease to MPS IIIA, neurocognitive function in MPS IIIB is not as well defined in older and more attenuated forms of the disease. In too many cases, clinical judgment of severity has taken the place of careful quantification of cognition, as Yogalingam [133] has pointed out. Unfortunately, no natural history studies of the rarest forms of MPS III, C and D, have been carried out. There is an urgent need to do this, as treatments are currently being developed.

The neurocognitive aspects of MPS IV and VI have of minimal focus except for a few studies. Both of these MPS types have neurocognitive abnormalities that have not been well defined. Measures of attention, executive function, memory and visual spatial function are more important than IQ for these patients. Any treatments that are developed will not easily affect overall intelligence, which is already consolidated by the time these patients are diagnosed. Rather, focusing on aspects other than IQ may provide a more sensitive indicator of possible change with treatment. Further, characteristic behavioral abnormalities such as been found in MPS IV, should be further investigated to clarify brain-behavior relationships and possibly provide an endpoint for a treatment trial. For these patients, treatment - or at least understanding of their neurocognitive deficits - needs further research and hypothesizing of possible treatment strategies. Finally, MPS VII, like MPS IIIC and IIID, is an extremely rare MPS type. However, in MPS VII, development of a peripheral therapy with a subsequent monitoring system has made possible the tracking of the natural history of cognition possible.

Up to this point, the natural history studies in the literature have been reviewed. There are not as many such studies as would be desirable. There are many challenges to carrying out such studies.

Multivariate and multicenter natural history studies, which are needed for rare diseases, are very expensive and require a considerable infrastructure [246]. They are usually beyond the capability of any single institution unless it is an expert center devoted to seeing such patients. Even then, most academic and clinical institutions do what can be done using information gathered from clinical visits. If rigorous protocols are used for clinical patients, such studies can contribute much to the field. However, many of most rigorous prospective longitudinal studies have been done by pharmaceutical companies seeking to collect data that will inform their clinical trials or as a historical control group. This is especially the case when sample sizes are small and diseases are rapid and lethal. Berry et al. [246] have recently described the importance and complexity of partnership of pharmaceutical companies and institutions for funding the study of rare diseases.

Another source of funding is programs like the NIH sponsored Rare Disease Clinical Research Network (RDCRN). The NIH funded the Lysosomal Disease Network (LDN) as part of the RDCRN first in 2008. The LDN included an MPS (I, II, and VI and IV - recently added) longitudinal study of brain structure and function (imaging and neuropsychological studies) which is now 12 years old. This study has produced a number of important published studies of neurocognition and behavior. While the RDCRN program provided limited funds for basic assessments, the research was co-funded by pharmaceutical companies, advocacy groups and foundations to support travel and other aspects not funded through NIH. This partnership allowed a significant multicenter infrastructure to be created, which will continue after the funding ends in 2023. The infrastructure created also was the foundation of other studies of MPS disorders and clinical trials.

Another challenge with natural history data is publication and data sharing. Many studies supported by pharmaceutical companies have collected data that remains unpublished and unavailable to other researchers. This invaluable natural history data needs to be in a central repository that is vetted and available to researchers. There have been calls to create such a central repository, notable by the recent Consensus Conference on cognitive endpoints [11].

This paper has reviewed the majority of the neurocognitive natural history studies of the MPS disorders and pointed out where further studies might be necessary. We also have addressed clinical trials of treatments that are designed to affect brain function. We hope this review will provide an impetus for further studies, with the intent of a better understanding of the disease course and associated influential factors, furthering treatment of these devastating diseases.

Declaration of Competing Interest

Elsa Shapiro, Ph.D. is the managing partner of Shapiro Neuropsychology Consulting through which she has received fees for providing consultation services on cognitive and behavioral endpoints.

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