

REVIEW ARTICLE

International working group identifies need for newborn screening for mucopolysaccharidosis type I but states that existing hurdles must be overcome

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ABSTRACT

Aim: Mucopolysaccharidosis type I is a lysosomal storage disorder that can result in significant disease burden, disability and premature death, if left untreated. The aim of this review was to elaborate on the diagnosis of mucopolysaccharidosis type I and the pros and cons of newborn screening.

Methods: An international working group was established to discuss ways to improve the early diagnosis of mucopolysaccharidosis type I. It consisted of 13 experts in paediatrics, rare diseases and inherited metabolic diseases from Europe and the Middle East.

Results: It is becoming increasingly clearer that the delay between symptom onset and clinical diagnosis is considerable for mucopolysaccharidosis type I and other rare lysosomal storage disorders, despite numerous awareness campaigns since therapies became available. Diagnosis currently depends on recognising the signs and symptoms of the disease. The practice of newborn screening, which is being explored by pilot programmes around the world, enables early diagnosis and consequently early treatment. However, these studies have highlighted numerous new problems and pitfalls that must be faced before newborn screening becomes generally available.

Conclusion: Newborn screening for mucopolysaccharidosis type I offers the potential for early diagnosis and early pre-symptomatic treatment, but existing hurdles need to be overcome.

INTRODUCTION

Mucopolysaccharidosis type I (MPS I) is a lysosomal storage disorder that can result in significant disease burden, disability and premature death if untreated. It is caused by α -L-iduronidase deficiency, recorded in the Online Mendelian Inheritance in Man (OMIM) database as OMIM 252800. It encompasses three syndromes: Hurler

Abbreviations

ERT, Enzyme replacement therapy; HSCT, Haematopoietic stem cell transplantation; MPS I, Mucopolysaccharidosis type I; MPS, Mucopolysaccharidosis.

Key notes

- A diagnosis of mucopolysaccharidosis type I often involves numerous physicians and several years' delay, and targeted symptom-based screening of at risk populations is of limited use.
- This paper presents the findings of an international working group that looked at how to improve the early diagnosis of mucopolysaccharidosis type I.
- They report that newborn screening appears very useful but various problems and pitfalls must be tackled before it becomes generally available.

(OMIM 607014) is the most severe, Scheie (OMIM 607016) is the attenuated form and Hurler–Scheie (OMIM 607015) falls between these forms (1). The principal pathological defect involves glycosaminoglycan catabolism, which leads to continuous accumulation of glycosaminoglycans and associated interference with cellular functions. The parents of children with MPS have been reported to express a range of concerns, including obstructive sleep apnoea, delayed language acquisition and associated communication difficulties, chronic pain, physical differences and restricted mobility and participation in social activities (2). Furthermore, the presence of musculoskeletal disease has a great impact on the quality of life of children with MPS (2).

MPS I is considered to be the most comprehensive form of MPS, as it displays a complete manifestation of all the signs and symptoms of MPS and the wide variability in disease severity. It was also the first MPS for which different treatments became available. For these reasons, MPS I serves as an example of disease management for all types of MPS. For children with the Hurler phenotype, the current standard of care is allogeneic haematopoietic stem cell transplantation (HSCT), which should be performed as soon as possible and definitely before 2–2.5 years of age (3,4). The disease also responds to enzyme replacement therapy (ERT) with laronidase, a recombinant human α -L-iduronidase, which was introduced in 2003, and has been reported to result in improved respiratory function, mobility and endurance (5–10). Since laronidase does not cross the blood–brain barrier, it has no effect on the brain. A combined approach using HSCT and ERT has been shown to be effective (11,12), but both treatments are less effective after the onset of clinical disease, as downstream or secondary consequences of disruption of glycosaminoglycan catabolism, such as cardiac valve disease and skeletal disease, generally do not improve when the pathological changes of MPS I are already established (9).

In order to gain treatment benefit, the first step is to diagnose individuals with MPS I. However, the clinical symptoms are initially non-specific and may involve many tissues and organs, contributing to a delay in diagnosis (1,13). An overview of the signs and symptoms is provided in Table 1, and specific examples are provided in Figure 1. Quantitative urinary glycosaminoglycan testing is generally available, and it is possible to use this as initial screening when there is clinical suspicion of MPS I. Although a positive finding of urinary glycosaminoglycan is most frequently diagnostic, a negative quantitative urinary glycosaminoglycan result, on its own, should not be used to exclude a diagnosis of MPS I. Additional biochemical evaluations should be carried out because urinary glycosaminoglycan levels may not be elevated in some cases, mainly patients with an attenuated form of the disease (14,15). Furthermore, there is no biochemical test that is currently available to distinguish between the different phenotypes in a completely reliable manner (16,17). A complete diagnostic evaluation for MPS I should

include referring the patient to a metabolic specialist and geneticist, and performing a combination of tests. These include quantitative and qualitative urinary glycosaminoglycan assessments, enzyme assays to evaluate α -L-iduronidase activity and genetic and molecular testing to determine disease severity and the appropriate treatment approach (15,18,19). Testing enzyme activity and genotype using the dried blood spot test provides a valuable fast approach to the diagnosis of MPS I (20–22), but the results must always be confirmed by traditional laboratory methods. Critically, earlier diagnosis leads to earlier treatment and better outcomes (9,23–25).

This consensus paper was developed by the European MPS I advisory board, which consisted of 13 MPS I experts from Europe and the Middle East who convened to discuss ways to improve the early diagnosis of MPS I. It discusses the pros and cons of introducing population screening of newborn infants for MPS I.

Pitfalls of clinical diagnosis or selectively screening for MPS I

MPS I is a rare disorder and many primary care physicians, who are the gatekeepers to specialist care in many countries, will probably not see a single case during the course of their career. Nevertheless, it is important to ensure that they have the necessary information, for example diagnostic algorithms or guidelines, so that they can diagnose rare conditions and make decisions about referring patients to suitable specialists (26). The decision-making process is particularly important, as healthcare systems frequently expect primary care physicians to refer patients to individual specialties for investigation and treatment of specific symptoms. As children with MPS I often present with clusters of symptoms involving several organ systems, such as joint disease and especially kyphosis, hernia, hepatomegaly and ear, nose and throat infections (Table 1), they may end up being referred to a number of different specialists. The process of diagnosis can, therefore, require multiple visits over many years, with patients seeing an average of five physicians before they receive a correct diagnosis (1).

The complexities in diagnosing MPS I are further illustrated by the number of different diagnoses and the consequent potential for misdiagnosis (1). The spectrum of diseases with similar signs and symptoms can be enlarged to include all other types of MPS, together with mucopolidosis and mannosidosis. Early symptoms, such as enlarged tonsils or hernias, commonly occur in the paediatric population; these symptoms, on their own, would not raise any suspicion of MPS I. It has also been noted that a diagnosis of MPS I becomes more challenging when the disease is less severe, with increased delays between symptom onset and diagnosis, as the symptom severity diverges from that typically seen in Hurler syndrome (13,27,28). In a case series, Cimaz et al. (29) found that an MPS I diagnosis could take many years in patients with an attenuated disease, because early symptom clusters may be difficult to recognise.

Table 1 Checklist of MPS I signs and symptoms. When one of these signs is present, check for other signs. MPS I should be suspected when at least two of the signs occur together.

Suspicious findings	Details
Airway obstruction	Obstructive sleep apnoea, snoring, macroglossia, gingival hypertrophy, difficulty with intubation
Cardiac valvular disease/ cardiomyopathy	Heart insufficiency/failure
Carpal tunnel syndrome	Mainly in children or young adults: bilateral and recurrent
Coarse facial features	Progressive (from mild to severe): large head, bulging forehead, thick lips, widely spaced teeth, large tongue and short, flat nose with wide nostrils. Not often typical in Hurler–Scheie and Scheie
Corneal clouding	Progressive visual impairment
Developmental delay	Initial symptom-free interval, then delayed acquisitions followed by a plateau and loss of previously acquired skills (only in the severe phenotype)
Dysostosis multiplex	Hip dysplasia, scoliosis, kyphosis, gibbus, genu valgum, odontoid hypoplasia
Family history	Sibling affected with MPS I
Growth retardation	Deviation from the growth curve, short stature
Hepatosplenomegaly	Enlargement of both the liver and spleen
Hydrocephalus	Mainly in severely affected patients
Inguinal and umbilical hernia	Mainly when bilateral (inguinal) or recurrent
Joint contractures or stiffness without inflammation	Thickening of joint capsules, contractures/stiffness of joints, progressive difficulties in performing daily activities, including walking
Psychiatric symptoms	In adults with attenuated phenotype
Repeated ear, nose and throat infections/upper respiratory tract infections in the first years of life	Recurrent rhinitis or otitis media in the first years of life – also occurring before social mixing and not necessarily related to concomitant infections in other siblings – hearing loss, early adenotonsillectomy, t-tubes
Spinal cord compression	Mainly cervical and thoracic
Trigger fingers	Progressive, hands and toes, short, broad hands with curving fingers

MPS I, mucopolysaccharidosis type I.

Finally, targeted screening for MPS I in selected populations with symptoms associated with the disease, such as ear, nose and throat disorders, hip dysplasia and hernias, is unlikely to be beneficial. This is due to the low incidence of the disease, the high frequency at which individual symptoms are observed in the population as a whole, and because symptoms should already be present before a patient is screened for MPS I.

Taken together, several factors contribute to delays in diagnosing MPS I, including the rarity of the disease, the non-specific nature of its symptoms, the need for differential diagnosis and the ineffectiveness of targeted screening.

The case for newborn screening

Therefore, we advocate the use of alternative screening methods, based on the increasing availability of dried blood spot enzymatic screening for MPS I and the potential for this disease to be added to newborn screening programmes alongside other metabolic diseases (30). Pilot newborn screening projects for lysosomal storage disorders have been implemented for Fabry disease, Pompe disease, Gaucher disease and Niemann–Pick diseases type A and B (31–34). Moreover, newborn screening programmes that include MPS I have been piloted in Taiwan (35,36), the United States – namely Missouri (34), Illinois (37) and Washington State (38) – Brazil (19) and some regions of Italy (39). All of these studies used dried blood spot sampling and α -L-iduronidase enzyme assays, although there were differences in the methodological strategies employed, with mass spectrometry (19,36,38), fluorometry (35,36,39) and digital microfluid methods (34) being used. The expected incidence of MPS I in an Australian study of over four million births over a period of 16 years was one in 100,000. This figure was based on the number of postnatal diagnoses divided by the number of births (40). However, incidence rates based on the above-mentioned newborn screening programmes are much higher (34,35,38), with one exception: a study that reported an incidence rate of one in 219,793 (37). These contradictory results might be partially explained by the fact that individuals carrying some benign variants, such as c.99T>G (35) and c.246C>G (38), as indicated by the ClinVar database (41), were initially listed as affected patients in some of these papers. On the one hand, this indicates the need for the early diagnosis of MPS I, with newborn screening being a suitable method, but on the other hand, it shows how delicate the screening issue might be.

Challenges of newborn screening

Newborn screening for MPS I is not currently available in all countries, and even where it is available, it still needs to be formally implemented into national health programmes in Europe. Although there is increasing evidence to support the early diagnosis and treatment of lysosomal storage disorders, such as MPS I (30), there are challenges associated with the implementation of newborn screening programmes. These include the need for an accredited method, or methods, for detecting α -L-iduronidase deficiency, achieving an acceptable level of false-positive results, and differentiating the severity of the disease (16). Molecular analysis currently enables researchers to differentiate between severe and attenuated forms of MPS I in less than 50% of cases, emphasising the need to identify other accurate, sensitive and reliable tests for differentiating disease severity in different patients (16,17,42). Assuming that an accredited test for evaluating enzyme activity in

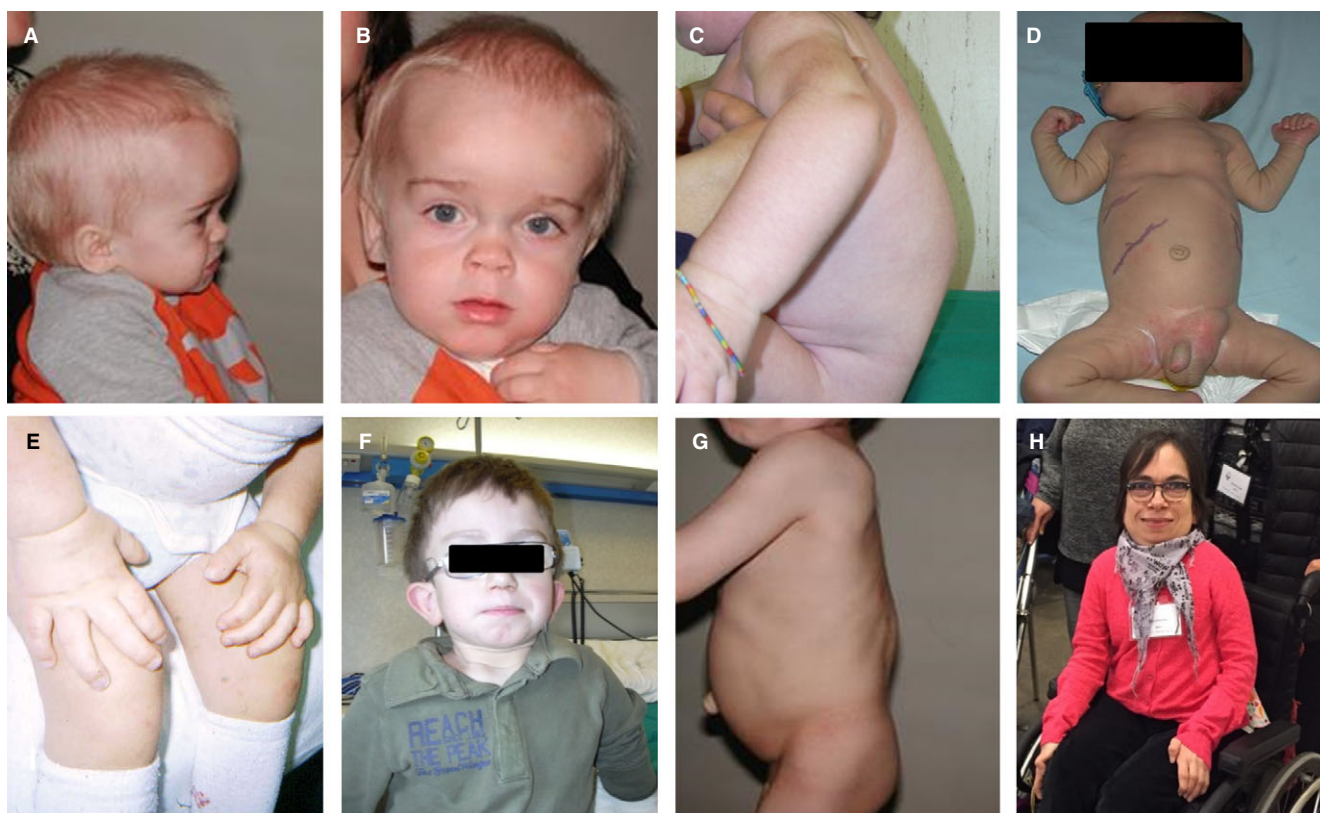


Figure 1 Characteristic features of MPS I. Facial expressions of a 16-month-old MPS I Hurler patient (A,B); gibbus in a 12-month-old MPS I Hurler patient (C); hepatosplenomegaly and inguinal hernia in a three-month-old patient with MPS I Hurler (D); claw hands in an 18-month-old MPS I Hurler patient pre-HSCT (E); A five-year-old patient newly diagnosed with MPS I Hurler–Scheie; note that the facial expressions are not typical (F); umbilical hernia and gibbus in a four-year-old MPS I Hurler–Scheie patient on ERT (G); paraparesis in a 40-year-old MPS I Scheie patient (H). ERT, enzyme replacement therapy; HSCT, haematopoietic stem cell transplantation; MPS I, mucopolysaccharidosis type I. Informed consent was obtained from all individuals or their guardians.

dried blood spot samples was available, newborn infants with activity levels below a pre-specified threshold would need to be referred for confirmatory enzyme assays, substrate accumulation assays and genetic analysis. Once a genetic variant has been confirmed, the relationship between the variant and the disease phenotype would need to be established. If the infant is carrying two common pathogenic variants with known severity in homozygosity or compound heterozygosity, the phenotype could be predicted (42).

A severe phenotype could also be predicted if the patient has two nonsense alleles (43). In this case, HSCT could be performed very early for patients with severe disease forms (44). If, on the contrary, the patient is carrying one or two rare or novel missense variants of unknown significance, the genotype would not help to predict the severity of the phenotype and new sensitive biochemical methods would have to be developed in order to reach a phenotype prediction in a newborn infant. To further complicate the scenario, there are variants of unknown significance that might or might not be pathogenic. A subgroup of these variants may also cause a pseudodeficiency, but not clinical symptoms (37,45). If one of these variants is associated with a true pathogenic variant, the enzyme test

would show severe deficiency in an infant who is only a carrier. In such a case, parents would be faced with substantial psychological and sometimes financial burden until a definitive diagnosis of pseudodeficiency had been made. This underlines the need for trained medical staff to manage parents' fears and expectations when the disease, in an apparently asymptomatic newborn infant, needs to be defined in terms of phenotype severity or when a patient is heterozygous for one pathogenic variant and a pseudodeficiency variant. In order to improve the newborn screening process, we need to identify best practice for proper communication, as it has been shown that effective communication, including access to educational resources, can alleviate parental stress and minimise psychosocial burden after false-positive newborn screening results (46,47).

Questions about possible treatments and patients' choices need to be explored. In cases where the pathogenic variants identified are already known to cause severe disease, decisions about treatment pathways may be relatively clear. However, in cases where variants are associated with a more attenuated phenotype, or when variants with unknown significance and unclear consequences have been identified, consensus recommendations on how to proceed

may be required. Decisions about watchful waiting with no treatment compared with the initiation of ERT may need to be made in less affected patients (30). To achieve the best outcomes for patients, the option of long-term treatment with ERT alone needs to be balanced against decisions on whether, or when, to proceed with HSCT while continuing ERT in the peri-transplant period (12,23).

CONCLUSION

It has been shown that early diagnosis of MPS I enables early treatment with HSCT or ERT, either alone or in combination, and can make a substantial difference to outcomes (9,23–25). Despite the availability of effective treatments, diagnosis continues to involve numerous physician visits and delays from symptom onset of several months for Hurler disease to several years for the attenuated form of the disease (1,48). At present, a diagnosis of MPS I in patients with uncommon symptoms, such as kyphosis and hepatomegaly, and, or, clusters of common symptoms presenting at an unusual age with an uncommon frequency and, or, pattern should be considered. However, it has been shown in the Netherlands that awareness campaigns targeted at medical doctors to provide them with access to tools for an early MPS diagnosis have not reduced diagnostic delays in the last 30 years (48). Newborn screening provides the earliest possible opportunity to diagnose this disorder. Evidence for the efficacy and feasibility of newborn screening continues to be gathered and a few pilot programmes to detect MPS I at birth are ongoing (34–36,38,40). Yet, with the exception of the Netherlands, where inclusion of MPS I in the local newborn screening programme has been recommended (49), routine national newborn screening programmes are unlikely to be implemented in the immediate future. We support the implementation of newborn screening based on the dried blood spot method to diagnose MPS I at birth. However, until newborn screening for MPS I becomes available, awareness of the clinical signs and symptoms that lead to a diagnosis of MPS I remains the only tool to reduce delays in providing specialist care and thus facilitating early treatment. When diagnosis through newborn screening becomes available in the future, as we hope will be the case, the complexity and pitfalls of this diagnostic means should not be underestimated. The medical community and general population should be well educated to face the different aspects of the disease and to avoid miscommunication that could potentially generate needless panic and incorrect treatment decisions.

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CONFLICT OF INTERESTS

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1 Conflicts of interest.