Neonatal Screening for MPS Disorders

Subjects: Pathology

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Newborn screening enables the diagnosis of treatable disorders at the early stages, and because of its countless benefits, conditions have been continuously added to screening panels, allowing early intervention, aiming for the prevention of irreversible manifestations and even premature death. Mucopolysaccharidoses (MPS) are lysosomal storage disorders than can benefit from an early diagnosis, and thus are being recommended for newborn screening. They are multisystemic progressive disorders, with treatment options already available for several MPS types. MPS I was the first MPS disorder enrolled in the newborn screening (NBS) panel in the USA and a few other countries, and other MPS types are expected to be added. Very few studies about NBS for MPS in Latin America have been published so far.

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1. Introduction

Newborn screening (NBS) allows for a reduction of morbidity and mortality of selected treatable disorders within the first few days of life, enabling early treatment of the newborns [1]. The beginning of NBS was in the 1960s, with the pioneering work of Robert Guthrie and Ada Susi, who have implemented a screening test for phenylketonuria (PKU) [2]. The benefits of NBS soon became clear, and a growing number of conditions were continuously added to screening panels to bring the benefits of early detection and early intervention to more and more babies [3]. This impact is so significant that the Centers for Disease Control and Prevention (CDC) considers NBS one of the ten great public health achievements of the 21st century [4], as it may proportion to the detected baby interventions and benefits such as prevention of developmental delay, severe disability, or even premature death [3].

Mucopolysaccharidoses (MPS) are progressive disorders that can potentially lead to death within the first decades of life due to severe clinical manifestations, such as neurological impairment, skeletal abnormalities, as well as pulmonary and cardiac problems [5][6]. Although there is still no cure for MPS, there are several treatment options already approved that could benefit most MPS patients. Diagnosis based on clinical suspicion usually takes a few years to be achieved [7], and there is already robust evidence about the benefits of early intervention [8][9]. Thus, advocacy for the addition of newborn screening for MPS led to the addition of MPS I by the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) to the Recommended Uniform Screening Panel (RUSP)

in February of 2016 [10][11]. Missouri was the first state to screen for MPS I [12], followed by several other states, and the state of Illinois has also started the screening of MPS II in 2017 [13][14][15], followed by Missouri in 2019.

A pilot study for the screening of MPS I was performed in Taiwan [16] in 2008, followed by a pilot study for MPS I and II [17], and then by a large-scale NBS program of MPS I, MPS II, and MPS VI in 2015 [18]. A pilot study for MPS IVA was also performed in Taiwan in 2013 [19]. Another pilot study was performed in the Tuscany and Umbria regions of Italy for MPS I [20], and also in the northeast of Italy [21][22]. MPS I and II NBS pilot studies were performed in Osaka [23], and a small feasibility study for NBS of MPS II was performed in the Netherlands [24].

Despite these major achievements, a wide-scale inclusion of lysosomal disorders (LSDs), such as MPS in the NBS program, is still moving slowly. The UK National Screening Committee (UK-NSC) does not currently recommend the inclusion of MPS I in their systematic population screening program [25], and this is no different in Latin America, where there is a considerable variation in the screening panels among different countries, and where standard neonatal screening is still not routine in several nations [26]. Comprehensive data about newborn screening in Latin America can be found in several surveys [27][28]. This paper provides a review of the pilot newborn screening programs for MPS performed in Latin America.

2. Discussion

Newborn screening has a clear impact on reducing the morbidity and mortality of several treatable disorders, aiding to decrease the disease burden in the patient's life and its effects on healthcare costs. To the best of our knowledge, until this moment, only Brazil and Mexico have started pilot studies for the implementation of NBS for MPS in Latin America. There are still several limitations for this implementation in Latin American countries: the limited budget of the countries for NBS programs, the limited capacity of NBS laboratories, prioritization of screening for more traditional disorders with higher incidence and best-known screening advantages, lack of awareness about the MPS as to the benefits of their early diagnosis/early treatment, and high cost of therapies for MPS.

Although only MPS I and MPS VI have been included in the pilots performed so far, the availability of methodologies for multiplex screening by LC/MS/MS for MPS II, MPS IIIB, MPS IVA, and MPS VII will allow the testing for these conditions, which have therapies already available or in development, to be added to pilot screening panels soon.

Other limitations that may be faced during the implementation of NBS for MPS, which are phenotypically very heterogeneous, are the challenges of predicting the phenotype, the choice of the most appropriate treatment for each case (ERT versus HSCT, and in a very short future, probably also ERT with fusion proteins, gene therapy, and gene editing), and the cost of the assays. The finding of VUS and pseudodeficiencies may also be a challenge if biomarker measurements (GAG analyses) are not performed . We should also mention the ethical issues related to the identification of carriers and genetic variants in other genes if large gene panels, exomes, or whole-genome sequencing are employed [29].

It is also important to note that enzyme assays by MS/MS or DMF are recommended to be the first-tier test, to avoid false positives [30]. A GAG assay in the same DBS could be performed as a second-tier test, but not as a first-tier test due to the high number of false positives (GAGs can also be elevated in other conditions) [31][32][33]. Some centers might prefer to perform sequencing as a second-tier test, but this could lead to unclear conclusions when a VUS is found. Thus, we recommend analyzing the enzyme as a first-tier test followed by GAGs in the same DBS (to avoid recollection and generation of parental anxiety), and then to perform molecular analysis. False positives can also be reduced by the use of post-analytical interpretation tools, such as the Collaborative Laboratory Integrated Reports (CLIRs) [33]. After the confirmatory testing, it is recommended to perform a follow-up with clinical evaluation and to start the appropriate treatment as indicated by the therapeutic guidelines. The interaction between the laboratory group and the clinical follow-up team is essential for the achievement of better outcomes [34].

Another important aspect to recommend is the conduction of pilot studies before the implementation of the screening program because they aid with validation, the establishment of cutoffs, estimation of costs, definition of program algorithms, and also provide useful information for governments to take the appropriate action [35].

3. Conclusions

Newborn screening targets conditions that are usually asymptomatic at birth, in which the introduction of therapy before the irreversible disease manifestations have occurred lead to a significant and positive change in its clinical course. New technologies of screening and therapy are driving the evolution of such screening to have more disorders added to the NBS panels. Nowadays, even complex diseases such as MPS become a potential target for NBS, and it now seems that it is just a matter of time before MPS screening will happen on a large scale worldwide, enabling early and timely identification and avoiding the long diagnostic odyssey that is experienced by most patients, whose treatment could only start years after patients become symptomatic and already have irreversible sequelae.

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