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Patients' perspectives on newborn screening for later-onset lysosomal storage diseases

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ABSTRACT

Lysosomal storage diseases (LSDs) are an individually rare but collectively common group of hereditary, progressive, multi-systemic disorders. Recent technological advances have brought newborn screening (NBS) for LSDs to attention in the United States. However, many LSD symptoms present in later childhood or adulthood, with a wide spectrum of severity. Because late-onset symptoms stray from the traditional NBS model, healthcare providers have expressed concerns about potential harm to patients and/or their families. In this study, 47 individuals with Fabry disease (FD), 22 with Gaucher disease (GD), and 22 with late-onset Pompe disease (LOPD) were surveyed regarding how their life might have been impacted by NBS. Of the 91 participants, none had symptoms at birth and 42 (46.7%) were symptom-free until adulthood. Over half (52.8%) were diagnosed ≥5 years from symptom onset; of these, significantly more had FD (60%) or LOPD (63.6%) than GD (23.8%). However, length of diagnostic odyssey was not significantly correlated with opinion on NBS. Most participants either strongly agreed (45%) or agreed (33.3%) with NBS for their condition, with no significant differences between diseases. Opinions on NBS were correlated with participants' opinions on whether NBS would have resulted in better current health, but uncorrelated with disease severity or current life satisfaction. Significantly more participants with FD (42.6%) and LOPD (63.6%) than GD (13.6%) felt they would have greater life satisfaction had they been diagnosed as a newborn ($p = 0.007$). Almost half (41%) of participants would have made different life decisions, including lifestyle, financial, and reproductive decisions. Regarding potential harm, participants were most concerned about insurability and least concerned about removal of children's autonomy. In conclusion, NBS is highly approved of among individuals with LSDs themselves, as it would significantly eliminate diagnostic odysseys and potentially alter life planning.

1. Introduction

Lysosomal storage diseases (LSDs) are an individually rare but collectively common group of hereditary, progressive, multi-systemic disorders. Technological advances in diagnosis and treatment have caused newborn screening (NBS) for LSDs to become a growing area of focus in the United States (U.S.). In 2006, New York became the first state to implement LSD NBS, passing legislation mandating NBS for Krabbe disease. In 2013, Missouri added several LSDs in addition to Krabbe disease to their NBS panel, including Fabry, Gaucher, and Pompe diseases and mucopolysaccharidosis type 1 (MPSI) [1]. Several other states have legislated for one or more LSDs on NBS since then. In addition, the Secretary for Health and Human Services recommended both Pompe and MPSI diseases be added to the Recommended Uniform Screening Panel in March 2015, as advised by the Discretionary Advisory Committee on Heritable Disorders in Newborns and Children [2].

Historically, the 1968 Wilson and Jungner criteria for population-based screening have guided decision makers in adding NBS conditions. Among these ten criteria are the availability of acceptable treatment, adequate understanding of disease natural history, and agreed-upon policy regarding whom to treat as patients [3]. Advances in treatment for some LSDs include enzyme replacement therapies (ERT), substrate reduction therapy (SRT), and hematopoietic stem cell transplant (HSCT). Both ERT and HSCT are more effective when initiated early in disease course, arguing for NBS for these LSDs [4–6]. Yet most LSDs have a spectrum of severity due to allelic heterogeneity, with residual enzyme activity or milder mutations leading to presentations in later childhood or adulthood. Unfortunately, NBS techniques cannot currently distinguish between infantile and later-onset forms of these conditions [5–8]. Genotype-phenotype correlations with enzyme analysis can

Abbreviations: LSDs, lysosomal storage diseases; FD, Fabry disease; GD, Gaucher disease; LOPD, late onset Pompe disease; MPS, mucopolysaccharidosis; NBSP, newborn screening perception questionnaire; BIPQ, brief illness perception questionnaire.

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help predict early- versus later-onset disease course but are available for only a portion of mutations in Gaucher disease (GD), limited in Pompe disease (PD), and typically not available in Fabry disease (FD) due to significant allelic heterogeneity [9].

It is unclear in later-onset forms of LSDs such as FD, GD, and late-onset Pompe disease (LOPD) when (or if) symptoms will begin and when treatment should be initiated. Because natural history is not clear regarding symptom onset and it is not evident who should be treated as patients, later-onset LSDs stray from the traditional NBS model of Wilson and Jungner [3]. Newborn diagnosis of later-onset diseases raises multiple ethical concerns, including increased parental anxiety, loss of autonomy for the child, increased medicalization (multiple healthcare appointments to determine if symptoms have begun), stigmatization, and health/life insurance discrimination [10–12]. While genetic healthcare providers (biochemical and medical geneticists, genetic counselors, and biochemical lab directors) are concerned about all of these potential effects, they are most concerned about potential health/life insurance discrimination and medicalization of the child [13].

It is not clear, however, whether those affected most by NBS for late-onset diseases (i.e. patients with LSDs and their families) share these ethical concerns. Weinreich et al. [14] surveyed the general public and family members of patients with PD in the Netherlands for their opinions on NBS for PD [14]. While they did not distinguish infantile from LOPD in participating families, they found 88% of family members and 87% of the general public were in favor of NBS for PD. Furthermore, 86% of family members and 80% of the general public felt detection of 3 to 5 infants with LOPD per year was acceptable, with family members being significantly less concerned than the general public about potential harm from NBS diagnosis of LOPD.

Hayes et al. [4] surveyed US and Australian support group members regarding NBS for mucopolysaccharidoses (MPSs). Respondents included parents of children with MPS (all types) (~96%) and a small number of adults affected with MPS (~4%). The vast majority of respondents (97%) were in favor of NBS with available treatment, with 87% and 84% in favor of NBS for severe or mild MPS respectively even without treatment, citing the avoidance of a diagnostic odyssey as an important benefit. Nineteen percent also mentioned reproductive risk knowledge for future children as a benefit. Only a small minority expressed concerns, including removing the carefree presymptomatic period with their children (7%), and altering parents' perceptions of their child (2%) [4]. A qualitative study [15] further demonstrated the importance of early diagnosis and treatment in the eyes of 13 parents of children with MPSI and 6 patients with attenuated MPSI.

While the above studies have explored the opinions of healthcare providers, the general public, and family members of patients, very few LSD patients themselves have been included in NBS research thus far. The present study asks the opinions of adults with late-onset LSDs on NBS for their condition and explores how they think NBS might have impacted their lives.

2. Materials and methods

2.1. Survey development and recruitment

The Newborn Screening Perception Questionnaire (NBSP) was developed by the first author and consisted of multiple choice and open-ended questions. Initial questions target demographic information, participants' diagnostic experiences, perceived severity of symptoms, and treatment experience. The survey then focused on participants' opinions of NBS and how their life might have been impacted by NBS (to extrapolate to current NBS conditions, subjects were asked to imagine treatment was available at the time of their birth). Though not formally validated, the NBSP was beta-tested with four certified genetic counselors with expertise in LSDs prior to use.

The Brief Illness Perception Questionnaire (B-IPQ) was developed and validated by Broadbent et al. [17] to measure current perception of disease severity. Possible scores range from 0 (no perceived illness) to 80 (highest perceived severity). The B-IPQ has established test-retest reliability, concurrent and predictive validity, and discriminant validity in several chronic diseases, including asthma, diabetes, and patients with a history of myocardial infarction [16,17].

Both surveys were mailed with an informed consent and cover letter invitation to 143 patients followed by the Emory Lysosomal Storage Disease Center (90 FD, 47 GD, and 6 LOPD). Additional LOPD patients were recruited via a Pompe disease-specific listserv (GSD.net, short for Glycogen Storage Disease.net). Subjects were also recruited during annual clinical visits or bimonthly infusion at Emory's LSD infusion center. The Emory University Institutional Review Board (IRB) reviewed and approved the study design, informed consent form, and surveys used.

2.2. Statistical methods

Data analyses were performed using SAS v9.4 (Cary, NC) and R Project v3.3.1 (Vienna, Austria). Statistical significance was evaluated at the $p = 0.05$ level unless otherwise specified. Patient demographics, genetic disorder characterizations, and item-level measure responses for the B-IPQ and NBSP questionnaires were summarized using means and standard deviations or frequencies and percentages as appropriate. All NBSP responses were evaluated both overall and by disorder type (FD versus GD versus PD); moreover, specific NBSP items of interest were associated with Total B-IPQ score and across other NBSP questions. An example would be “How would you classify your disease symptoms right now (NBSP Question 7)?” versus “How satisfied are you with your life right now (NBSP Question 9)?” Concurrently, statistical differences for the NBSP questionnaire both across genetic disorder levels and against other NBSP items were calculated for categorical responses using Chi-square tests of independence or Fisher's exact tests; one-way analysis of variance (ANOVA) tests were performed for continuous items. For categorical response comparisons, when statistical significance was found across genetic conditions (FD versus GD versus LOPD), pairwise comparisons were calculated at a significance level of 0.017, after adjusting for multiple comparisons using a Bonferroni correction ($0.05/3 = 0.017$); likewise for continuous items, post-hoc adjustments were made using the Tukey-Kramer method. Bar charts and tables were used throughout to represent pertinent statistical relationships.

3. Results

A total of 91 subjects participated in this study. Of the 143 questionnaires sent by mass mail, 39 were returned (28.5% response rate). The remaining 52 participants were recruited during clinic, infusion appointments, or through GSD.net. Of the 91 participants, 13 returned only the NBSP questionnaire, resulting in a total of 91 NBSP questionnaires and 78 B-IPQ questionnaires. Results are presented below.

Demographic data is presented in Table 1. Participants averaged 46.4 years of age (SD $\pm$ 14.7 years), with the majority being Caucasian (87.9%). Most participants (80.3%) had at least some college education. Half of participants (51.7%) had FD, 24.2% had GD, and 24.2% had LOPD, reflective of the patient population at the study team's institution.

As measured by the NBSP, 46.7% of participants developed symptoms after 18 years of age, 43.3% between 5 and 18 years old, and 10% prior to age 5. When stratified by disease, significantly more LOPD patients (63.6%) and GD patients (59.1%) developed symptoms after 18 years of age than FD patients (32.6%)($p = 0.019$), with FD patients varying in symptom onset between 5 and 10 years (37%), 10 and 18 years (23.9%), and >18 years of age (32.6%). None of the subjects had symptoms at birth, confirming the definition of later-onset LSDs as defined by NBS parameters.

More than half of participants (52.8%) waited over five years from symptom onset to diagnosis (Fig. 1). When stratified by disease,