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Original Article

The benefits of newborn screening for cystic fibrosis: The Canadian experience

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Abstract

Background: The impact of newborn screening (NBS) for cystic fibrosis (CF) on early indicators of long-term health was evaluated in the context of government-sponsored healthcare and access to current therapies.
Methods: Using data from the Canadian CF Registry between 2008 and 2013, we compared the rates of respiratory infections and markers of nutritional status in those diagnosed through NBS to those who were diagnosed clinically within the same time period using Mann–Whitney and Fischer's exact test as appropriate.
Results: The study included 303 subjects, 201 in the NBS group and 102 in the non-NBS group. NBS patients were diagnosed earlier and had their first clinic visit at a younger age. Pancreatic insufficiency was less common in NBS patients. The incidence of *Pseudomonas aeruginosa* and *Staphylococcus aureus* were lower in NBS patients. After adjusting for age at clinic visit, gender, pancreatic status, and *Pseudomonas aeruginosa* infection status, mean *z*-scores for weight-for-age and height-for-age were higher in NBS patients, with no differences in BMI-for-age.
Conclusions: NBS programs for CF lead to improved long-term health outcomes for the CF population.

Keywords: Newborn screening; Hospitalization; Nutritional status; Growth; Infection

1. Introduction

There is overwhelming evidence that supports the establishment of newborn screening (NBS) programs for cystic fibrosis (CF) to improve the overall survival, long-term growth and health outcomes of people living with CF [1–3]. NBS programs for CF have been widely adopted in several European countries, Australia, New Zealand and the majority of North America — with the exception of Quebec (QC) and Mexico [4–7]. NBS most often consists of a two-step screening test using immunoreactive trypsinogen (IRT) from a blood spot procured during the first few days of life that is followed by a search for common mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, although other approaches exist. A positive CF screen results in a referral to a CF clinic to confirm the diagnosis through additional blood and sweat testing. Babies with a high risk of having CF are identified and once the diagnosis is confirmed, education and treatment is initiated, typically in the first 4 to 6 weeks of life.

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The benefits of NBS for CF have been studied in other parts of the world and reported in 2005 [3,8]. In the US, between 1988 and 2013, there have been major improvements in both nutritional status and lung function in young children [9]. This may be due to a combination of early diagnosis through NBS and intervention, including mucolytic therapy, aggressive treatment of infection with *Pseudomonas aeruginosa* (*P. aeruginosa*), and aggressive nutritional supplementation to prevent malnutrition. Recognition of the need for early intervention in regards to treatments such as nutritional support, early eradication of *P. aeruginosa*, and airway clearance has resulted in improvements in clinical factors in young CF patients, such as lung function and nutritional status [10]. It is currently unknown if these interventions could mitigate the consequences of later diagnosis and diminish the benefits of newborn screening.

In Canada, NBS for CF was first introduced in the province of Alberta (AB) in April 2007, followed by Ontario (ON) a year later in April 2008. The screening algorithms differ slightly between AB and ON [11]. In AB, the IRT cutoff is >60 μg/L or 98th percentile and in ON, it is the 96th percentile. In both cases, this is followed by genetic testing using the TM Biosciences Tag-It 39+3 mutation kit. The diagnosis of CF is typically confirmed when two disease causing mutations are identified along with a sweat chloride value >60 mmol/L. QC is the last province in Canada that has not committed to adding CF testing to their NBS program. The objective of this study is to compare health outcomes in the first 6 years of life in children diagnosed through NBS in AB and ON, with children born in QC who did not have access to NBS. This comparison will allow us to evaluate the potential effects of NBS on early clinical outcomes specifically within the Canadian context where non-screened children would have the benefit of government-sponsored access to healthcare and medications. To our knowledge, this is the first study conducted to evaluate the impact of NBS programs for CF in Canada.

2. Materials and methods

2.1. Data source

There are 42 accredited Canadian CF clinics found in all provinces with the exception of Prince Edward Island and the three territories. All CF clinics receive annual incentive grants from Cystic Fibrosis Canada (CFC) to support and enhance their clinical services that are contingent on submitting patient data to the Canadian CF Registry (CCFR). The CCFR is a patient registry and has been in existence since the early 1970s and currently contains over 110,000 annual records on more than 7100 unique individuals with CF who have attended a CF clinic in Canada. It is estimated that the majority of the Canadian CF population is represented within the CCFR, giving a comprehensive picture of the CF population in Canada.

The CCFR data undergo routine validation checks to ensure that they are free of errors. Discrepancies are resolved by directly contacting the reporting CF clinic so that the raw data can be reviewed and unusual data can be confirmed or revised. All individuals within the CCFR have provided informed consent for having their data collected and used for research purposes. This study was approved by the Research Ethics Board of Montreal Children's Hospital and the CCFR oversight committee.

Patient data from the CCFR collected between January 1, 2008 and December 31, 2013 were used in this study. During this time period, the CCFR only captured data on patients with a confirmed diagnosis of CF based on current guidelines [12]. Longitudinal clinical measurements such as height and weight, were recorded from the first stable visit of the year while other variables such as microbiology, pancreatic status, genotype, number of hospitalizations, length of hospital stay, and other CF-complications reflect events that occurred within the calendar year. Lung function is typically measured reliably at 6 years of age and older; therefore, lung function measurements were not included as an outcome for this study.

2.2. Study cohort

The study included two groups of patients followed from 2008 to 2013: (1) infants diagnosed through NBS in AB and ON identified as the *NBS group*; and (2) the *non-NBS group* comprised of children diagnosed with CF in QC. Subjects were followed for a maximum of 6 years to reflect the starting date of the NBS program for CF in both AB and ON. In the CCFR, the upper limit of 6 years for diagnosis covers more than 80% of Canadian CF patients, and those diagnosed after 6 years of age are more likely to have milder forms and thus may not benefit from NBS. Children in QC diagnosed prenatally, due to an affected sibling, or presenting with meconium ileus were excluded, as these circumstances would increase the likelihood of an early diagnosis and they would be unlikely to benefit from an NBS program. With respect to microbiology, once a subject was found to have a positive respiratory sample for a bacteria, they were categorized as positive for all subsequent years in the analysis. Subjects who never had a specimen culture taken were removed to avoid misrepresenting their infection status. We categorized patients into three genotype classifications: homozygous for F508del, heterozygous for F508del and other.

We examined multiple health outcomes of early clinical factors that have been well-established as key indicators of long-term health outcomes in CF [13]. The primary outcomes of this study were markers of nutritional status, specifically weight-for-age, height-for-age and BMI-for-age measurements. World Health Organization (WHO) growth charts were used for all calculations [14,15]. Secondary outcomes included the incidence rate of infection with *P. aeruginosa* and *S. aureus*; the number of hospitalizations; and length of hospital stay.

2.3. Statistical analysis

Demographic and baseline characteristics between the NBS and non-NBS groups were compared using the Mann–Whitney test for continuous variables and the Fisher's exact test for categorical variables. We used generalized estimating equations (GEE) model and generalized linear mixed models (GLMM) to evaluate differences in health outcomes over time between the