

Shining new light on newborn screening of cystic fibrosis in the province of Quebec

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ABSTRACT

Newborn screening of cystic fibrosis, a severe genetic disease with high treatment burden, is offered in all of North America with the exception of the province of Quebec. This condition, when diagnosed on symptomatic presentation, is marked by chronic infections and progressive lung function decline leading to eventual respiratory failure. Patients continue to have a median age of survival notably below the Canadian average. Despite prevalence rates of cystic fibrosis almost three times the national average in certain regions of Quebec, the province still does not offer screening to its newborns. However, the results of newly published research comparing patients from Quebec with those of other provinces has shown that screening is associated with better nutritional status and overall growth, lower hospitalization rates as well as fewer episodes of infection, hence contributing to the prevention of lung damage in the long term. This research appears to confirm the benefits and pertinence of implementing a neonatal screening program for patients with cystic fibrosis in the province.

KEY WORDS: Cystic fibrosis; neonatal screening; respiratory insufficiency; quality of life

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Cystic fibrosis (CF) is an autosomal recessive disease associated with multiple organ systems dysfunction which most often declares itself in early childhood. As years pass, young patients suffer from progressive lung function loss, sinus disease and pancreatic insufficiency, among other conditions. While the Canadian national prevalence of the disease in 2008 was 1 affected child for every 3600 births, the latest numbers available for the province of Quebec reported a more elevated rate of 1 in 3030 births.^{1,2} The reported rates can at times go as high as 1 affected child in 902–935 births in some regions of the province, such as in Saguenay Lac St-Jean, mostly due to the founder effect and a carrier rate of 1:15, with some mutation variants suggestive of a more severe form of the disease.^{2,3}

CF remains to date a severe genetic condition with significant treatment burden, especially in North American and European populations.⁴ Based on data from the Canadian Cystic Fibrosis Registry of 2013, the Canadian median age of death was estimated at 50.9 years and of the 40 patients who died that year, half were under the age of 35.1 years.⁵ One of the major causes of morbidity during the course of illness is malabsorption, which leads to malnutrition and growth retardation. Recurrent infections contributing to worsening bronchiectasis and obstructive pulmonary disease are other complications of CF. With time, infections become chronic and microorganisms become resistant to treatment, leading to prolonged hospitalization times which are not only costly to the medical system, but also detrimental to school attendance and normal child development.⁶ Eventually, respiratory decline progresses to death in the absence of lung transplant. Even in the event of transplant, the median survival after surgery tends to be limited to 5.2 years for children.⁷

NEONATAL SCREENING PROGRAMS

As summarized in a 2012 INSPQ report,⁴ pilot projects for CF screening were initiated as early as in the 1980s in Australia, New Zealand and France, and by the turn of the century, many other European countries as well as the United States joined and established national newborn screening (NBS) programs. As these nations developed their programs, they released reports highlighting certain potential issues of screening. The main concerns emphasized by experts in the UK were the diagnosis and management of children with rarer mutation variants or atypical forms of the disease, as well as the insufficient evidence in the literature that screening improved lung function and overall clinical outcome.⁸ Yet, after considering the overall benefits of screening many countries deemed them sufficient to recommend the programs. Examples of benefits listed by the Health Council of the Netherlands included a more efficient diagnosis process and earlier access to services for families, improved nutritional status of patients, and parents who are better informed for future reproductive planning.⁹ Moreover, there was later evidence that the expense of NBS for CF is less than that of clinical diagnosis.¹⁰

In 2007, Alberta became the first province in Canada to establish an NBS program, following a pilot study where data were collected about the disease's incidence and characteristics, the tests' validity and the required follow-up.⁴ Other provinces and territories soon

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followed suit and in 2010 the Canadian College of Medical Geneticists recommended that every province introduce an NBS program for CF.¹⁰ At present, screening is offered everywhere in North America, with the exception of Quebec.

THE PROTOCOLS

In terms of testing, the screening consists most often of two steps. First, a blood spot is obtained in the first few days of life to measure immunoreactive trypsinogen (IRT). Then, a second IRT sample is done or a search is undertaken for common mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. If this yields a positive screen, patients are referred to specialized clinics for further testings, namely the sweat chloride test, to confirm the diagnosis. With such early diagnosis, treatments can be initiated at as early as 4–6 weeks of age.

However, because there is no consensus in the scientific community on the ideal IRT threshold value and since the panel of genetic mutations tested are adapted to local populations' ethnic backgrounds, there exists great variability between protocols, even within the same country.¹⁰ As no superiority of a methodology has yet been demonstrated, IRT threshold levels have been decided according to the sensitivity and sensibility desired for a first and then second sample, values that in turn depend on the resources available as well as the predetermined acceptable false positive rate.⁴ Panels of mutations have been chosen depending on epidemiological characteristics and frequency of mutations, but also on the willingness to diagnose atypical and asymptomatic cases.¹⁰ Screening for CF also results in the detection of false positives, bringing forth the issue of potential stress for families. Indeed, parents with children who have received a positive result for CF screening followed by a negative diagnostic workup report anxiety after the initial news, yet this negative psychological impact seems to resolve within three months.¹¹ Hence, the effect of false positive results must be weighed against that of prolonged misdiagnosis in affected children and its costs.

THE QUESTION OF QUEBEC

Quebec remains the only province in Canada that does not provide access to NBS. Without screening, median age at diagnosis in the province is 6 months, with 31% of patients being diagnosed after age 1, mainly due to the misdiagnosis of atypical or milder cases that present with non-specific symptoms.⁴ Moreover, diagnosis on the basis of symptoms rather than NBS more than doubles the rates of hospitalization and number of complications for patients.¹² In 2012, l'Institut national de santé publique du Québec (INSPQ) was given a mandate by the government to study the question of NBS using the WHO criteria for pertinence of universal screening programs.^{4,13}

The criterion of responding to a recognized need is easily met as there is a predominance of the disease in Quebec, surpassing the Canadian average, especially in regions such as Saguenay Lac St-Jean. Although the criterion of availability of a cure is not yet reached for CF, the chief objective of screening would revolve around preserving pulmonary function and nutritional status as long as possible to maximize chances of eventually responding to curative treatments still in their early stages of development.¹⁴ Additional benefits would be reducing misdiagnosis and its costs in consultations and hospitalizations, alleviating stress and negative

psychological effects for parents, and providing adequate counselling for family planning.

The challenges of tailoring a protocol in the current context of significant variability between methodologies and the difficulty of determining a panel of mutations for the local population and its evolving immigration patterns are not unique to Quebec. Essentially, if NBS were to be adopted, these values would have to be rigorously determined based on a study of the province's population. However, this study could build upon the data bank initiated in the context of the Canadian Consortium for Cystic Fibrosis Genetic Studies, which has already collected the genotypes of 45% of the province's patients.³

Children identified by the NBS could be readily referred to the centres in the province that offer specialized multidisciplinary care for patients affected by CF. Evaluation of the effectiveness of the screening program could be done along with assessment of the quality of care provided by these centres. Thereby, the process of quality assessment, a weakness highlighted by the INSPQ report, could benefit from improvement.

In spite of all the aforementioned favourable conditions, the INSPQ concluded at the time that evidence was lacking to issue a recommendation in favour of the NBS for CF. Their analysis of the available scientific evidence deemed it inconclusive, mostly due to poor quality research yielding inconsistent and contradicting results, although NBS for CF was proven to respect the eligibility criteria of screening of Wilson and Jungner.⁴

NEW RESEARCH

However, research has since emerged that could shed new light on the issue. Mak and his team at McGill University led a retrospective study comparing the health outcomes of children diagnosed with NBS in Ontario and Alberta ($n = 201$) with those of children born in Quebec ($n = 102$) with no access to screening.¹⁵ The results showed that the screened patients had better nutritional status and overall growth, lower prevalence of *Pseudomonas aeruginosa* and *Staphylococcus aureus* infections, and lower hospitalization rates than those who were diagnosed later in life. As such, this study appears to demonstrate that early diagnosis and intervention do contribute to prevention of irreversible lung damage, hence confirming that access to recognized management strategies in the province of Quebec cannot match the benefits of systematic NBS programs. We argue that this recent report finally brings forth the information that should tilt the table in favour of universal NBS for CF in Quebec.

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RÉSUMÉ

Le dépistage néonatal de la fibrose kystique, une maladie à forte charge de morbidité, est offert partout en Amérique du Nord sauf au Québec. Diagnostiquée une fois l'apparition de symptômes, cette maladie est caractérisée par des infections chroniques et un déclin de la fonction respiratoire menant à une éventuelle insuffisance respiratoire. Malgré un taux de prévalence jusqu'à trois fois plus élevé que la moyenne canadienne, la province n'a toujours pas de programme de dépistage de la fibrose kystique pour ses nouveaux-nés. Cependant, une nouvelle étude comparant les patients du Québec à ceux d'autres provinces au pays démontre que le dépistage est associé à de meilleurs états nutritionnels et niveaux de croissance ainsi qu'à de plus bas taux d'hospitalisations et d'infections, contribuant à prévenir la détérioration pulmonaire au fil des années. Ainsi, cette étude semble confirmer les bénéfices et la pertinence de l'implantation d'un programme de dépistage néonatal pour la fibrose kystique dans la province.

MOTS CLÉS : fibrose kystique; dépistage neonatal; insuffisance respiratoire; qualité de vie