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Commentary

Why screen newborns for profound and partial biotinidase deficiency?

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Newborn screening for biotinidase deficiency is currently performed throughout the United States and in many countries of the world. However, there are still many countries that do not screen for the disorder. After learning how many countries are still not screening for biotinidase deficiency, and after I received the comments on a recently submitted publication, I was compelled to address two major concerns about newborn screening for the disorder. The first is why should a country screen their newborns for profound biotinidase deficiency (less than 10% of mean normal serum enzyme activity)? The second is, if a country screens their newborns for profound biotinidase deficiency, why should they also screen for partial biotinidase deficiency (between 10% and 30% of mean normal serum enzyme activity)?

Before addressing these issues, I would like to state that over the past 32 years, my research has focused on the study of the clinical, biochemical and molecular aspects of biotinidase deficiency. Even though my laboratory developed the colorimetric assay for biotinidase activity using blood-soaked filter paper cards, and we conducted the first newborn screening program in Virginia, I have not received, nor do I currently receive, any compensation for any aspect of newborn screening of the disorder. This being said, I would like to address the above questions.

Why screen newborns for profound biotinidase deficiency?

Since the discovery of biotinidase deficiency in our laboratory in 1982 [1,2], there has been a rapid transition from the development of a colorimetric method for determining biotinidase activity using blood-soaked filter paper spots [3] to the demonstration of the feasibility of performing the first newborn screening program for the disorder [4], to its incorporation into the newborn screening program of all states in the United States and in many countries [5]. The latter is best explained by the fact that biotinidase deficiency readily met the major criteria for inclusion of a disorder into a newborn screening program:

- The disorder can cause severe neurological or cutaneous symptoms, which may progress to coma or death, if not treated.
- The disorder can be effectively treated with a simple, inexpensive form of therapy; oral biotin. Moreover, there is no known toxicity of the vitamin.
- Symptoms of the disorder can effectively be prevented with early biotin treatment.
- The disorder can result in irreversible neurological abnormalities, such as cognitive deficits, hearing loss and vision problems, even after the disorder is diagnosed in symptomatic individuals and then treated.
- Children with the disorder do not usually exhibit symptoms immediately after birth, but usually at several months of age, and can even initially develop symptoms in adolescence or adulthood.
- The methods of newborn screening are inexpensive and have appropriate specificity and sensitivity for identifying enzyme-deficient individuals.
- Primary care physicians and other health professionals usually are not familiar with the disorder and routinely do not include it in their differential diagnoses; even genetic and metabolic specialists have missed diagnosing the disorder.

In fact, a group of experts in newborn screening was convened by the American College of Medical Genetics to develop a uniform screening panel. To do this, questionnaires were sent to geneticists and metabolic experts around the country to rate various criteria of 84 different disorders to determine a disorder's appropriateness for inclusion in a newborn screening panel. In 2006, the results of the survey were published [6] and biotinidase deficiency ranked fifth of the 84 disorders as best meeting these criteria behind medium-chain acyl-CoA dehydrogenase deficiency, congenital hypothyroidism, phenylketonuria, and neonatal hyperbilirubinemia.

It is clear from the available information that a child with profound biotinidase deficiency is at major risk of developing symptoms, including cognitive disability, hearing loss and optic atrophy, which are usually irreversible if they occur prior to biotin treatment [7]. However, even with what is being reported for the natural history of the disorder around the world and the experiences of the vast majority of states and countries, there are still many countries that have opted not to

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incorporate biotinidase deficiency into their newborn screening programs [8]. In the executive summary, of 29 member states of the European Union, candidates, potential candidates and European Free Trade Association countries, only 10 perform newborn screening for biotinidase deficiency. In the survey, the participants report that they use multiple factors to consider inclusion of a disorder into their screening programs. A majority of the countries use the criteria set forth by Wilson and Jungner [9] in 1968 for deciding which disorders to screen. These criteria include validity, reliability, yield, cost, acceptance and follow-up services. A majority of the countries also use guidelines of scientific societies, literature surveys and/or national scientific research in their consideration. In addition, most countries use epidemiological evidence (i.e., incidence of the disorder) or economics as the strongest arguments for adding a disorder to their screening program, although many consider ethical arguments for inclusion. The survey also indicated that the major reason for exclusion of disorder was economic or the lack of epidemiological evidence.

Surprisingly, France and the United Kingdom are two countries that do not screen their newborns for biotinidase deficiency. In fact, both countries perform newborn screening for very few disorders, six and nine, respectively, compared to the much larger number screened for in the United States and in other European countries [8,10].

France just recently added medium-chain acyl-CoA dehydrogenase deficiency to their newborn screening program [11]. Their decision to include this disorder into their program was based on a cost-effective analysis. The analysis stated that even though they did not know the true incidence of the disorder in France, they estimated it to be similar to that of neighboring countries. The French National Authority for Health (HAS) considered cost-effectiveness "to be an important element to inform policy decision even though France has not defined any incremental cost-effectiveness ratio threshold for the implementation of new public health interventions [11]."

A true cost-analysis for determining if a disorder should be included into a screening program considers many factors, such as how easy or inexpensive the testing method is, how inexpensive the treatment is, what are the morbidities and costs of the morbidity if a child is not identified as having the disorder, how easy it is to follow a child's progress as long as the child remains on therapy, savings from not having to visit specialists and to perform tests in an attempt to establish the correct diagnosis, etc. These latter reasons seem to be the most frustrating to the geneticists, metabolic specialists and parents of affected children. Decisions to exclude the disorder are often simply based on assumptions and without plans to gather the appropriate information, such as the true incidence of the disorder in a specific locale. Even, if the incidence of biotinidase deficiency in France or any country is lower than that of other disorders that that country screens, a true cost-analysis will appropriately consider all the factors in order to make an informed decision about inclusion or exclusion from a screening program.

As far as I am aware, such an approach has not been performed for biotinidase deficiency in France. This may be due to the assumption that the incidence of the disorder is too small to warrant consideration. If this is true, this seems to be speculation, and no actual pilot screening data are available. Without such data or at least consideration of the incidence of biotinidase deficiency in neighboring countries [12–15], if known, a cost-analysis cannot be appropriately performed in the country.

In the United Kingdom, the incorporation of a disorder into their national screening panel must be approved and recommended by their United Kingdom National Screening Committee. Biotinidase deficiency was considered several times and most recently in July 2013 [16]. The Committee has repeatedly not recommended that biotinidase deficiency be added to their newborn screening program for the following major reasons [17]:

1. "We do not know how common the condition is in the United Kingdom and how many babies are likely to be born with the condition in the future."
2. "While some people with the condition are badly affected, some remain well into adulthood and others never show obvious signs of being poorly. A better understanding of why the condition affects people different ways is needed if treatment is to be directed to those who need it."
3. "The current test is not suitable for large numbers of babies. Research into different tests is at an early stage and more information is needed."
4. "Some countries offer screening for biotinidase deficiency but others don't. The lack of people with the condition has led to some countries withdrawing the screening programme."

I will address each of their points:

First, the advisory group has stated that the incidence of the disorder is not known in the United Kingdom; however, it seems simple and obvious that the only way for them to answer this question is to perform a pilot screening program and determine its incidence. Otherwise, this will always be an unresolved issue in the United Kingdom or in any other locality where the incidence becomes a major or the major factor for incorporation into a screening program.

Second, the United Kingdom National Screening Committee's statement that "a better understanding of why the condition affects people different ways is needed if treatment is to be directed to those who need it" is a "catch-22" trap. Soon after the discovery and the initial characterization of the disorder, we became aware of the variability of expression of symptoms and the age they first occurred in untreated affected individuals, even within the same family and the siblings obviously had the same genotype [18–20]. As stated above, symptomatic individuals can develop significant neurological damage that may be irreversible after they are shown to be enzyme deficient and then are treated with biotin. Some individuals develop symptoms during infancy, most during early childhood and others not until later childhood or adolescence. In addition, clearly some children with profound biotinidase deficiency who became non-compliant with taking their biotin, particularly during adolescence, will develop symptoms [20,21]. Granted, there are a few individuals of varying ages who are discovered to have profound biotinidase deficiency but are asymptomatic [22,23]. However, these asymptomatic individuals are clearly the exceptions rather than the rule. In fact, there are multiple examples of adult-onset, enzyme-deficient individuals with a variety of inherited metabolic diseases [24,25], including phenylketonuria [25,26]. We routinely admonish those individuals who are enzyme deficient and are not taking biotin that they may be at risk of developing symptoms, and it is probably most prudent for them to consider taking the vitamin, even as adults. Although we may not understand the epigenetics or reasons for this variability, an untreated child with profound biotinidase deficiency appears to be a "time bomb" just waiting to become symptomatic.

Importantly, in the case of biotinidase deficiency, clinicians, geneticists and metabolic specialists frequently fail to make the diagnosis in a timely fashion before irreversible damage has occurred. With many countries screening for the disorder, our window of opportunity to study the natural history of the disorder is becoming smaller. This is due in part because there was a relatively short time from the discovery of the disorder to the incorporation of the disorder into many screening programs. It is obvious that the more countries that screen for the disorder, the more difficult it will be to ever satisfactorily answer this query of the committee. In addition, this query was not completely answered for most, if not all, other disorders, such as phenylketonuria, when they were incorporated into most newborn screening programs. In fact, we do know much about the natural history of profound biotinidase deficiency. We know that all untreated individuals with profound biotinidase deficiency are at considerable risk of developing major, potentially irreversible, symptoms if not diagnosed and treated in a timely fashion.