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AN APPROACH TO NEWBORN SCREENING

Developed by Ashton Cox and Dr. Shailly Jain for PedsCases.com.
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Introduction:

Hello, my name is Ashton Cox, and I am a 4th year medical student at the University of Alberta. This PedsCases podcast outlines an approach to newborn screening and was developed in collaboration with Dr. Shailly Jain, Associate Professor in the Department of Medical Genetics at the University of Alberta.

Learning Objectives

After this podcast, you should be able to:

1. Discuss the process and the rationale for newborn screening in Canada
2. List the variety of conditions that are screened for in different regions of Canada
3. Describe the clinical consequences and initial treatment of phenylketonuria
4. Outline the causes, symptoms, and initial treatment for congenital hypothyroidism

Clinical Case

Let's get started with a clinical case. Imagine you are a fourth-year medical student completing an elective in a family medicine clinic in Edmonton, Alberta. You are seeing Samantha, a 29-year-old G1P1 female, and her 3-day-old son Caleb. Samantha has been called in today because Caleb's newborn screen results came back positive for phenylketonuria. Your preceptor has asked you to discuss these results and the next steps with Samantha, as well as answer any questions she may have.

You complete a quick history and physical examination. Samantha and Caleb are both well. You then sit down with Samantha to disclose that Caleb's newborn screening test came back positive. Understandably, Samantha has several questions for you.

"I know that they took some blood from Caleb's heel in the hospital, but I wasn't too sure what they were screening for."

“What happens now that the test results are positive?”

“What is phenylketonuria? What does this mean for Caleb’s health and his future?”

Before we answer Samantha’s questions, let’s address our first learning objective. We will start by discussing what a newborn screen is, the origins of newborn screening in Canada, and the current process of obtaining a newborn screen.

What is Newborn Screening?

Newborn screening is a program that aims to identify certain severe and/or potentially life-threatening conditions early in the newborn course, in order to provide adequate treatment as soon as possible. Remember that *screening tests* are different from *diagnostic tests* -- screening tests are done for patients without symptoms, whereas diagnostic tests are done in a symptomatic patient and are targeted towards those symptoms. Newborn screening is a public health initiative and since its implementation, it has altered the natural course of many of the screened conditions.

Newborn screening is done by collecting a blood sample from all newborns in the hospital, generally by heel-prick shortly after birth. A midwife or pediatrician may also take a sample in the case of a home birth. Blood is spotted on a specialized card (referred to as a blood spot card) and sent to a designated laboratory for the indicated screening tests. Most provinces have just one laboratory where all provincial samples are sent, although some provinces may have more than one lab.

The beginnings of newborn screening in Canada can be traced back to Prince Edward Island, which was the first province to implement a program in 1963. Most provinces across Canada had followed suit and introduced screening panels by 1970. However, to this day there is no universal screening program across Canada, which means that each province and territory has its own process and its own list of conditions that are screened for.

Broadly speaking, the categories that are included in a newborn screening panel may include inborn errors of metabolism, endocrine disorders, hemoglobinopathies, immunodeficiency, cystic fibrosis, or critical congenital heart defects.

Some of the commonly screened conditions include:

- Congenital hypothyroidism
- Congenital adrenal hyperplasia
- Cystic fibrosis
- Phenylketonuria
- Sickle cell disease

It's important to note that this is not an exhaustive list, but just a few examples of what may be screened for. Currently in 2021, the number of screened disorders varies from 7 to over 40, depending on the province or territory. You can check out the most recent 'Newborn Screening in Canada Status Report'[2] to see the full list of conditions that are included in your area. You can also check on the official health website of your province or territory.

Let's now discuss two conditions that are included in newborn screening in all provinces and territories across Canada: phenylketonuria and congenital hypothyroidism.

Phenylketonuria

One condition that is included in every newborn screening panel across the country is phenylketonuria (PKU). Babies with PKU are deficient in the enzyme phenylalanine hydroxylase. This means that they cannot break down the amino acid phenylalanine which is found in foods that have protein, including breast milk and infant formula. In PKU, phenylalanine gradually builds up in levels that are toxic to an infant's developing brain. This can result primarily in intellectual disability, but other clinical features may also include seizures, behavioural abnormalities, microcephaly, and skin disease. As it takes time for phenylalanine to build up, children remain asymptomatic early on. Therefore, early detection and treatment is very important for successful management of PKU.

The newborn screening panel tests the serum concentration of phenylalanine. An elevated serum concentration is suggestive of PKU, but does not mean that an infant has PKU for certain. For any positive screening test, follow-up diagnostic testing is required to confirm the diagnosis. Newborns should be referred to a specialist for continued work-up.

Newborns are less likely to develop adverse health effects if they begin treatment by 3 weeks of age. The treatment for PKU is a life-long modified diet that is low in phenylalanine. There are infant formulas available that do not contain phenylalanine. Dieticians are an essential resource for dietary modification and management. Sometimes, the medication Sapropterin may also be used as an adjunct to a low phenylalanine diet.

Early diagnosis and treatment typically allows children with PKU to have normal growth and development. In this way, newborn screening has had an enormous impact on the well-being of babies with PKU and their families.

Congenital Hypothyroidism

Another condition that is included in newborn screening panels across Canada is congenital hypothyroidism. Congenital hypothyroidism (CH) occurs when an infant is born with a deficiency of the thyroid hormone. The etiology is heterogeneous, but the

majority of causes are related to the thyroid gland itself, such as an absent thyroid gland, a smaller than normal thyroid gland, or a gland that develops in the wrong location. A smaller number of cases may result from defective synthesis of thyroid hormone by the thyroid gland.

The incidence of congenital hypothyroidism in Canada is estimated to be approximately 1:2000 to 1:4000 infants. Most newborns with CH are asymptomatic. Some of the features that may develop include poor feeding, constipation, a puffy face, a hoarse cry, or jaundice. If not treated, CH can cause intellectual disability with delayed achievement of developmental milestones and poor growth.

The newborn screening panel detects if there is an increased serum TSH concentration. High TSH is suggestive of hypothyroidism. Just as we discussed with phenylketonuria, this initial positive screen does not necessarily mean that an infant has CH, but instead suggests that diagnostic testing is required. The diagnosis of CH is confirmed with a serum TSH concentration and a free T4 level. In some cases, an ultrasound or thyroid scan may be done. This imaging can help to determine the underlying cause of CH, for instance an absent or displaced thyroid gland.

The primary treatment for congenital hypothyroidism is replacement of the deficient thyroid hormone. Oral levothyroxine, or Synthroid, is the most commonly used medication. This is a lifelong treatment that should be started as soon as possible to prevent symptoms and health consequences from developing.

Back to Our Case

Now that we have more information, let's return to our clinical case and answer Samantha's questions about her 3-day-old son Caleb.

She first asked you, **"I know that they took some blood from Caleb's heel in the hospital, but I wasn't too sure what they were screening for."**

With your knowledge that different regions across Canada have slightly different screening guidelines, you are able to explain broadly that you are testing for inborn errors of metabolism, endocrine disorders, hemoglobinopathies, immunodeficiency, and cystic fibrosis. As you are completing your elective in Edmonton, you also direct Samantha to several resources that list Alberta's guidelines and the specific conditions that are tested in her province in case she wants to read more information.

Her next question was, **"What happens now that the test results are positive?"**

You recall that Caleb's screen was positive for phenylketonuria. You are able to explain to Samantha that this does not necessarily mean that Caleb has PKU, but that more testing will need to be done. Caleb will be referred to a specialist to continue his

work-up and care. It will take some time to get the results back and you acknowledge that this waiting period may be difficult for the family.

Finally, Samantha asked you, **"What is phenylketonuria? If Caleb does have it, what does this mean for his health and his future?"**

You explain to Samantha that phenylketonuria is a deficiency in the enzyme phenylalanine hydroxylase, which means that a child's body is not capable of breaking down the amino acid phenylalanine that is found in protein-containing foods. You let her know that high phenylalanine can have significant effects on a child's developing brain, but with special infant formula and a proper lifelong diet low in phenylalanine, PKU should not impact growth and development.

Samantha is grateful that you have taken the time to answer her questions so thoroughly, though she is anxious about the waiting period and the possibility that Caleb has PKU.

It is a few years later and you are now a family medicine resident in the same clinic in Edmonton. You are once again seeing Samantha and now 2-year-old Caleb for a routine well-child visit. After reviewing Caleb's chart and examining him, you find that his initial phenylketonuria results from 2 years ago did indeed come back positive. Caleb is now on a modified diet for his PKU, but overall has grown into a happy and healthy toddler.

Key Learning Points

Let's summarize some of the key learning points from this PedsCases podcast on newborn screening:

- Newborn screening aims to identify a specific set of neonatal or childhood onset conditions in the asymptomatic newborn stage in order to provide early treatment and avoid serious health consequences.

- Screening first came to Canada in Prince Edward Island in 1963 and was adopted more broadly across the country by the early 1970s. Canada does not have a universal screening program and as such the list of screened conditions varies by region. This information can be found in the most recent Newborn Screening in Canada Status Report,[2] or on the official health website of each province or territory.

- A few of the conditions that are screened include congenital adrenal hyperplasia, congenital hypothyroidism, cystic fibrosis, phenylketonuria, and sickle cell disease, among many others.

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- Screening is generally done by heel prick between 24 hours to 7 days of life. These results are forwarded to the infant's primary care provider. An initial positive screen does not necessarily mean that a child has a condition, but denotes that confirmatory testing is required. The child may be referred to a specialist for this additional testing and follow-up.

- Phenylketonuria is a deficiency in the enzyme phenylalanine hydroxylase. Infants with PKU cannot break down phenylalanine and this can cause intellectual disability. All provinces screen for PKU, which can be treated with a lifelong modified diet.

- Congenital hypothyroidism occurs when an infant is born with a deficiency of the thyroid hormone. CH is treated with lifelong levothyroxine (Synthroid).

- Early detection and treatment have vastly changed the natural history of many of the disorders included in the newborn screening panels. Treatment is able to prevent intellectual disability, poor growth, delayed developmental milestones, and many other adverse effects. In this way, the implementation of newborn screening has been a major public health success that has positively altered the lives of patients and their families.

Thank you for listening to this PedsCases podcast on newborn screening. I hope you enjoyed listening. Stay tuned for more PedsCases podcasts in the future!

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Resources

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