The Importance of Family History in Pediatric Primary Care

Overview
Family history information is obtained at various times in the care of a child in a residency continuity clinic or pediatric medical home. Although a comprehensive 3-generation family history is often considered the gold standard, primary care providers (PCPs) usually obtain less information, owing to time restrictions in the clinic. A more-targeted, or tailored, approach to a family history on the basis of a patient’s presentation or life stage allows the PCP to “think genetically” and gather appropriate information with the greatest impact for the patient. A continuity clinic or medical home can be expected to be the best setting to collect this information, and should be sure to make optimum use of this information.

Learning Objectives
Upon completion of The Importance of Family History in Pediatric Primary Care, residents should be able to

- use family history information to aid diagnostic considerations,
- consider a patient’s family history to maximize anticipatory guidance for potential serious issues or complications, and
- identify possible therapeutic interventions based on a patient’s family history.

Case Presentation
Initial Presentation
Charlie presents at 4 years of age for his regular checkup. The nurse notes that his stature is below the 3rd percentile.

ACGME Sub-competencies / Developmental Milestones Addressed

- **Patient Care**: Gather essential and accurate information about the patient
- **Practice-based Learning and Improvement**: Identify strengths, deficiencies, and limits of one’s knowledge
- **Professionalism**: Develop awareness of limitations to engage in help-seeking behaviors
- **Systems-based Care**: Coordinate patient care within the health system
Question 1. As you start your evaluation and consider his short stature, which one of the following factors is the least important to consider?

(A) His growth pattern since birth  
(B) The heights of his parents  
(C) His newborn screening results for thyroid abnormalities  
(D) Whether there is a family history of short stature  
(E) His newborn screening results for cystic fibrosis

At the initial stage of your evaluation of Charlie (while you are obtaining his past medical history), answers A–D are relevant to the issue of short stature. Charlie’s growth pattern since birth is an important indicator of whether his short stature is congenital or acquired and, if it is acquired, when the deceleration in growth began. Parental heights will assist in this evaluation also. Newborn screening for thyroid abnormalities should have been completed in the newborn period but it should be double-checked given his short stature. Family history of short stature is important. As will be emphasized below, additional family history information will also be critical, and “thinking genetically” will expand the diagnostic possibilities beyond just short stature. Although cystic fibrosis screening results are certainly important for Charlie’s health, presentation with short stature in the absence of respiratory or gastrointestinal problems make cystic fibrosis highly unlikely.

You start to think through diagnostic possibilities as you are obtaining Charlie’s medical history.

Question 2. Which of the following is the most important element of Charlie’s medical history?

(A) Prenatal history  
(B) Perinatal/newborn history  
(C) Social history  
(D) Family history  
(E) None of the above

All the elements of Charlie’s medical history (history of present illness, past medical history, past evaluations and medical records, developmental history, social history, family history) are equally important. Any attempt to take shortcuts and not obtain complete information during the evaluation of a 4-year-old child with short stature is fraught with the possibility of significant errors, inadequate evaluation, and inappropriate referrals. Never lose sight of the big picture.

Past Medical History and Family History
Charlie weighed 5 pounds 3 ounces (2.35 kg) at birth after a 39-week gestation. His 17-year-old mother was primigravida, weighed 125 pounds prior to her pregnancy, and struggled with maintaining an appropriate weight gain during the pregnancy. She smoked a pack of cigarettes per day. Mild hypertension was noted late in the third trimester along with trace proteinuria. The delivery was vaginal after the spontaneous onset of labor. No labor or delivery complications were noted. The placenta was noted to be “small.” The newborn exam was normal except for a small-for-gestational-age weight. Charlie grew slowly over the first 2–3 years of his life. There was some concern about his hearing, and his development was delayed. The initial family history recorded in his chart was “negative” except for some adult-onset diseases (cancer, diabetes, and hypertension).

Physical Examination
At his 4-year-old checkup, Charlie’s height is below the 3rd percentile; his weight is at the 5th percentile; and his occipital frontal circumference is at the 97th percentile. His slow growth was
presumed to be related to familial factors (his mother is “short”). Physical examination reveals coarse features with thick lips, thick alae nasi, periorbital puffiness, and full cheeks. He has mild kyphosis and stiff hands. No corneal clouding is found. There is some liver and spleen enlargement. There is also concern about his intellectual development. His neurological exam does not reveal any localizing findings. You suspect one of the mucopolysaccharidosis (MPS) disorders, which are a group of metabolic disorders.

**Question 3.** Which of the following statements is true?

- (A) The diagnosis of MPS is straightforward and does not require involvement of specialists.
- (B) **Discussing with the family the need for further evaluation and referral to a geneticist is the appropriate next step.**
- (C) The negative family history makes a metabolic condition unlikely because most of the MPS disorders are autosomal recessive.
- (D) The diagnosis of an MPS disorder has only limited impact on management because no specific treatments are available.

As the medical home provider, you should start preparing the family for a potential protracted diagnostic process and should arrange for genetic evaluation. Express your concerns to the family and let them know that you are there to support them through the process. The diagnosis involves a multifaceted approach (clinical evaluation, thorough family history review, and various other evaluations, including radiography, biochemical analyses, enzymatic analyses, and molecular analyses) that is best handled by specialists. A negative family history is not unusual for a metabolic condition with autosomal recessive inheritance; however, you should not just assume that the family history is in fact “negative” until it has been reviewed thoroughly. A specific diagnosis in the case of an MPS disorder is important because therapeutic modalities are now available in many cases to deal with the underlying disorder and various associated complications.

**Question 4.** On the basis of the medical history described above, you realize that you should take which of the following actions?

- (A) Consider further evaluation by a genetics team
- (B) Obtain a more-complete family history
- (C) Prepare the family for a complex situation
- (D) Make sure your office staff understands the potential difficulties in the management of this patient and prepares accordingly
- (E) **All of the above**

Even though you will be arranging for a genetics referral, as the PCP, you should take a complete family history and start engaging the family and your office staff in the team-oriented approach to a potentially complex situation. Initiate a conversation with the geneticist and his or her team to see what can be done while the evaluation is underway.

**Family History**

You re-reviewed his family history. The initial family history taken on the routine office forms in the first 6 months of Charlie’s life revealed cancer and diabetes on the mother’s side and multiple relatives with hypertension on the father’s side. A maternal uncle of the patient had died in his teens, but the family did not like to talk about it, and the mother did not know this brother.
Your more-thorough family history now reveals that the deceased uncle had a similar course and was diagnosed with a “mucopolysaccharidosis or MPS-problem” at a medical center out-of-state. You construct the pedigree below.

The family history information later obtained at the genetics referral revealed even more information than was obtained in various previous visits.

**Pedigree**

![Pedigree Diagram]

- High blood pressure
- Diabetes mellitus
- Colon cancer

**Question 5.** Which of the following should have been considered initially in the pediatric office?

(A) The collection of targeted family history information about similar or associated problems for several generations, as soon as problems such as short stature were noted
(B) Delayed referral to genetics because none of the problems noted were life-threatening
(C) An evaluation for genetic problems, starting with a microarray analysis
(D) Bone-age X-rays to assess bone age/chronologic age/height age

A more-thorough family history, targeting issues regarding stature and potentially related problems, is the first logical step in the evaluation. Such information will be very important in the assessment of the patient and in deciding on further testing or referrals. If the parents do not recall any problems within the family history, it is important to ask them to get further information from other family members and report that information back to you. The information about the deceased uncle is highly significant, and it is very likely that the maternal grandparents will be able to provide more information about that problem.

A negative family history does not rule out a genetic condition and may be seen in autosomal recessive conditions, autosomal dominant conditions, or X-linked conditions with reduced
penetrance. The problems noted in Charlie’s case point to a significant underlying diagnosis and call for early and prompt evaluation. Genetics referral should be considered early on for a timely diagnosis and prompt intervention. Microarray analysis is not indicated as a primary test in this case, especially because a metabolic problem is suspected. If the diagnostic features in this case were solely developmental delay, short stature, and dysmorphic facies, microarray analysis should be considered as a first-line test. However, the combination of developmental delay, short stature, coarse facies, kyphosis, hand stiffness, and mild hepatosplenomegaly point to another approach first. Bone-age films can help in the evaluation of short stature but are not a primary test at this stage. You could argue that if these studies (bone-age films) were done, the diagnosis of MPS would likely have been suspected. Flattening of the vertebrae or, in case of bone-age studies, beginning signs in the epiphyses of fingers of what later becomes more obvious dysostosis multiplex are frequently found before the clinical findings are apparent. In fact, radiographic studies can be helpful in MPS disorders with little to no coarseness, such as Sanfilippo syndrome.

**Diagnostic Testing**

After a genetic evaluation, Charlie was diagnosed with Hunter syndrome on the basis of the history and physical examination, radiographic studies, metabolic studies, enzyme analysis, and gene testing.

- Radiographic studies subsequently revealed some degree of dysostosis multiplex (signs of skeletal dysplasia with abnormal mottling of the bones).
- Sequential testing of urine studies for mucopolysaccharide analysis, enzyme analysis for iduronate-2-sulfatase, and DNA analysis for the specific mutation present (done by the genetics team) confirmed the diagnosis of Hunter Syndrome. These tests are best left to the specialist for deciding on the appropriate tests, analysis, and initial counseling.

**The Role of “Genetic Thinking” in Diagnosis, Prevention, and Treatment**

**Diagnosis**

Charlie has Hunter Syndrome, mucopolysaccharidosis type II, which is an X-linked recessive disorder. A careful review of the family history early on would have suggested an X-linked recessive problem and would have prompted a thorough and expedited evaluation of Charlie’s “growth” problems.

**Prevention**

An early diagnosis for Charlie is important, both for him and for his family. His mother is a carrier for Hunter syndrome, as indicated by the family history of an affected male in her lineage. Because she is a carrier, she has a 50% risk of having another affected male. We tend to think that making a diagnosis is pertinent only for the care of the patient, but in this case, the diagnosis of Hunter syndrome has significant reproductive consequences for the family and might influence their reproductive decision-making.

**Treatment**

Specific therapeutic interventions (enzyme replacement, hematopoietic stem cell transplantation, or both) are undergoing extensive investigation and have shown promise in some circumstances. An early diagnosis is critical if these therapies are shown to diminish or prevent some of the severe debilitating problems encountered in Hunter syndrome.
**Summary**
Charlie’s prenatal circumstances might have affected his immediate care in the newborn period. Because he had no significant health problems in the newborn period and he thrived into early infancy, this information is likely to be assumed to be irrelevant for his care. The early signs of growth problems, hearing loss, and abnormal physical features should have been clues calling for more-thorough evaluations before the age of 4. The family history of an uncle dying in his teens was a big red flag indicating a problem in the family and suggests an X-linked condition, given that the affected uncle was the mother's brother. The family history information should have been highlighted in Charlie’s medical record to make sure that he was followed closely for problems such as growth, development, or morphologic abnormalities. Abnormalities in all three of these spheres of involvement were present in Charlie’s case.

**References**

**Resources for Parents and Caregivers**
Hunter Patients. [www.hunterpatients.com](http://www.hunterpatients.com)