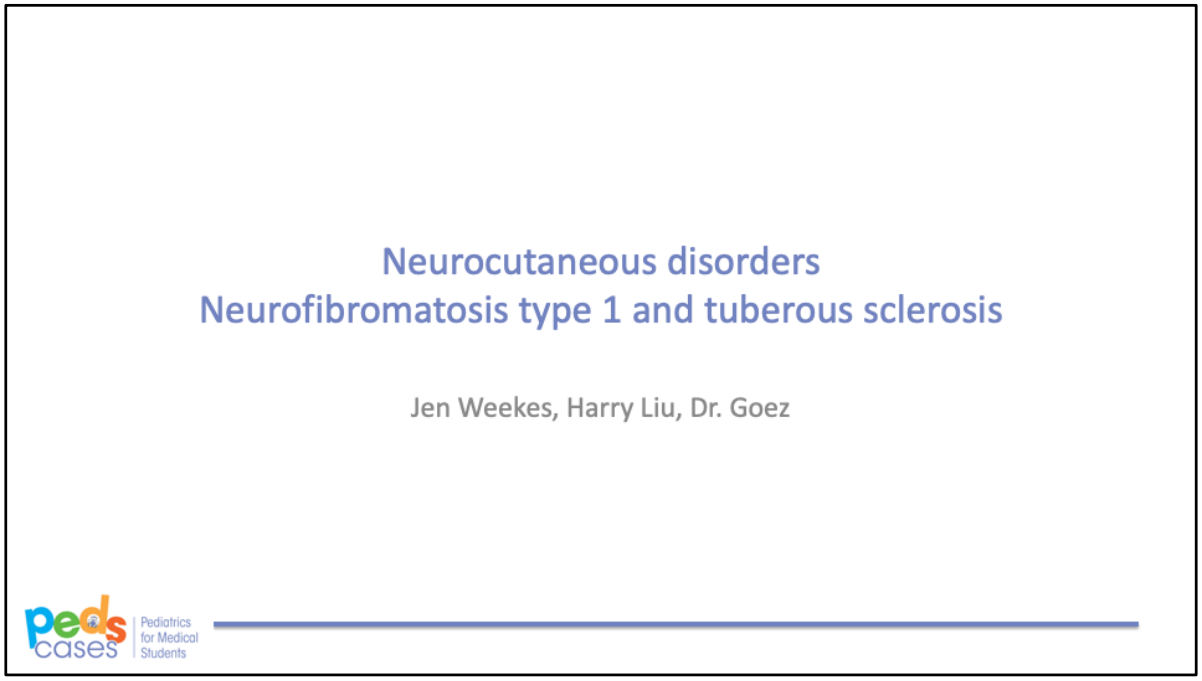
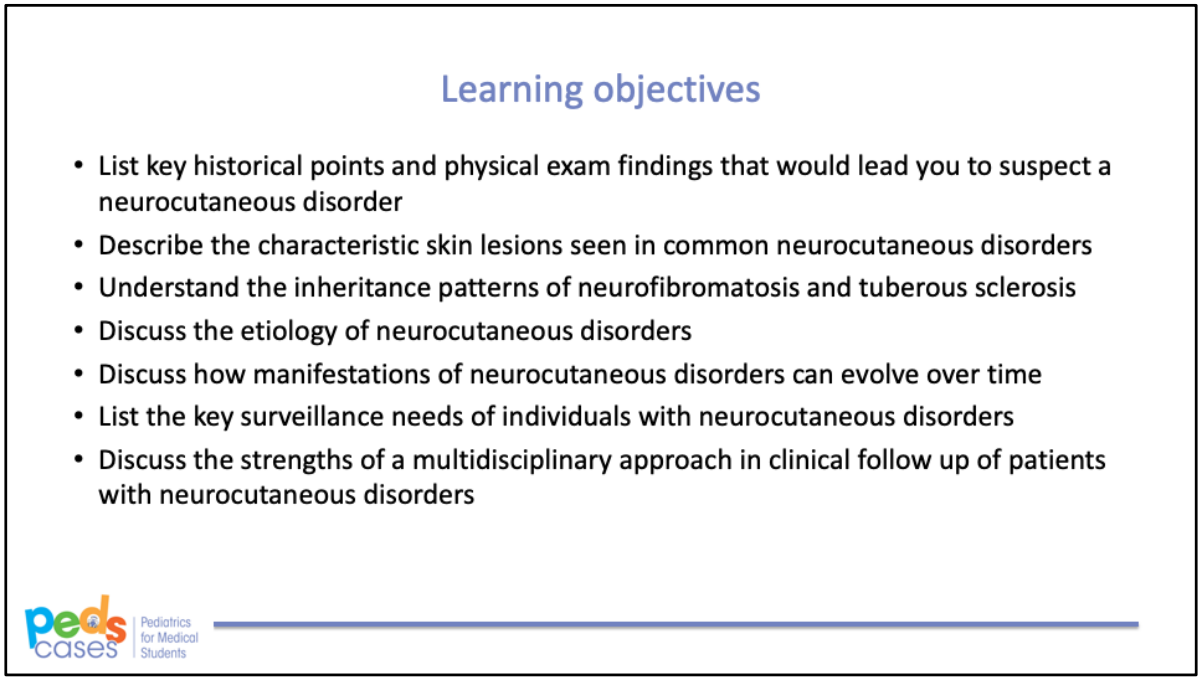


Slide 1: Introduction

Welcome to “approach to neurocutaneous disorders”, a podcast made for PedsCases.com at the University of Alberta. I am Jen Weekes. I am Harry (Chaocheng) Liu. We are both medical students at the University of Alberta. This podcast is made for medical students, and gives an organized approach to neurocutaneous syndromes. We’d like to thank Dr. Helly Goez for helping us develop this case. Dr. Goez is a pediatric neurologist at the Stollery Children’s Hospital and the Glenrose Rehabilitation Hospital in Edmonton, AB, Canada.



Slide 2: Objectives

List key historical points and physical exam findings that would lead you to suspect a neurocutaneous disorder

Describe the characteristic skin lesions seen in common neurocutaneous disorders

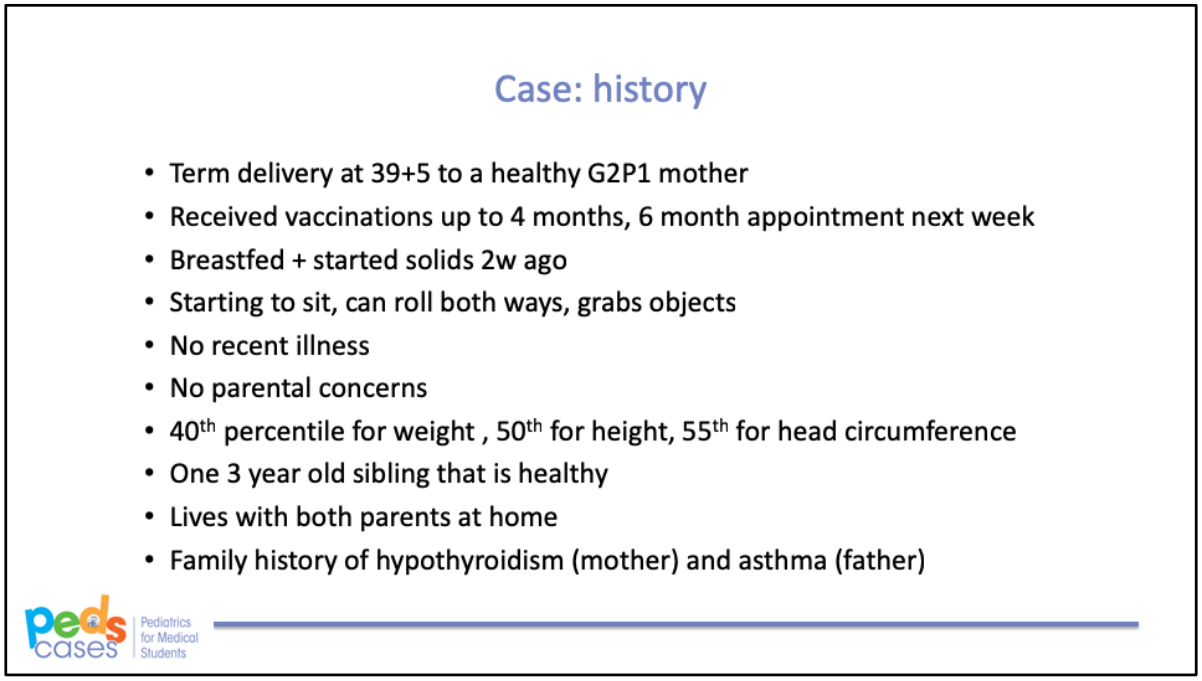
Understand the inheritance patterns of neurofibromatosis and tuberous sclerosis

Discuss the etiology of neurocutaneous disorders

Discuss how manifestations of neurocutaneous disorders can evolve over time

List the key surveillance needs of individuals with neurocutaneous disorders

Discuss the strengths of a multidisciplinary approach in clinical follow up of patients with neurocutaneous disorders



Slide 3: Case

Let's start with a case. You are a third year medical student on your pediatric rotation at a community clinic. You are asked to do a well-child check on a 6-month-old male. You start with the history. Here is what you find out:

Term uncomplicated delivery at 39 weeks and 5 days to a healthy G2P1 mother.

He received vaccinations up to 4 months, and his 6 month appointment is next week.

He is breastfed and started solid foods 2 weeks ago.

Starting to sit, can roll both ways, grabs objects, started babbling.

No recent illnesses or any parental concerns.

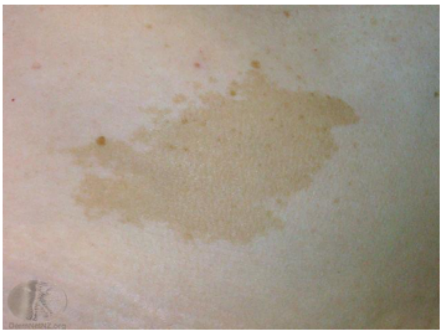
He is at 40th percentile for weight, 50th for height, 55th for head circumference.

He has one sibling who is 3 years old and healthy. He lives with both parents at home.

His father has asthma, his mother has hypothyroidism. The rest of family history is unremarkable.

Case: physical exam

- Skin exam
  - 5 café au lait spots
  - Range from 0.6cm to 1.2 cm in diameter



https://www.dermnetnz.org/topics/cafe-au-lait-macule/

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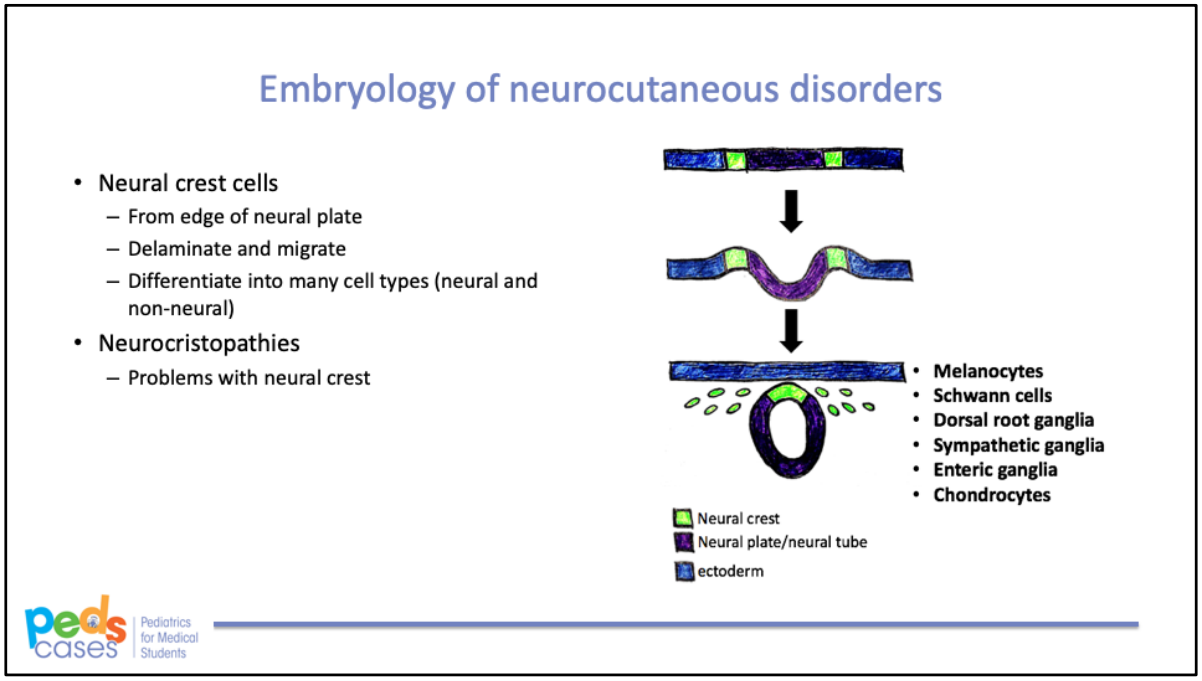
Slide 4: Case Continued

You move on to the physical exam. You begin with a head to toe inspection. To your surprise, you notice 5 skin lesions on the baby's torso. They are a bit darker than the rest of the skin and range in diameter from 0.6 cm to 1.2 cm. They are flat and irregular in shape. You ask the mother about them, she says they have been there since birth. Here is a picture of one of the skin lesions.

This is a 1.2 cm x 0.5 cm discrete uniformly pigmented light brown lesion with well-demarcated but irregular border located on the right lower quadrant of his abdomen. Based on the morphology of the macule, you immediately think of cafe-au-lait spots. You remember that café-au lait-spots are associated with some neurocutaneous disorders. Let's review neurocutaneous disorders briefly starting with the embryology and genetics of neurocutaneous disorders.



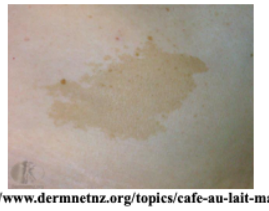
Slide 5: Embryology of Neurocutaneous Disorders
Neural crest cells are ectodermal cells that arise from the edge of the neural plate. When the neural tube forms, neural crest cells delaminate and migrate away from the neural tube and differentiate into multiple cell types including smooth muscle cells, chondrocytes, melanocytes, neurons and Schwann cells.

Neurocutaneous disorders belong to a larger group of disorders called neurocristopathies, disorders that arise due to problems with neural crest cells. As you can see in the diagram, neural crest cells can differentiate into a wide variety of cells and migrate throughout the developing body, which is why neurocutaneous disorders present with a range of phenotypes with multiple organ systems affected.

Today we will focus on the two most common neurocutaneous disorders: neurofibromatosis and tuberous sclerosis.

Neurofibromatosis overview

- **Neurofibromatosis 1 (NF1)**
  - Most common (1:3000)
  - AD; most de novo
  - neurofibromin gene (tumor suppressor)
  - Presents in childhood



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- **Neurofibromatosis 2 (NF2)**
  - AD; most de novo
  - Merlin gene (tumor suppressor)
  - Presents in early adulthood

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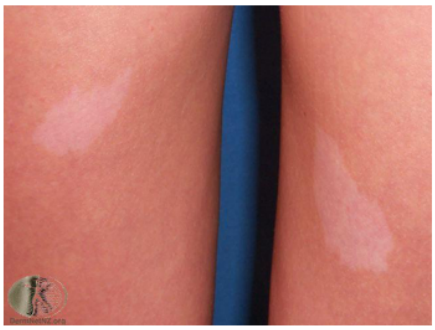
Slide 6: NF overview

Neurofibromatosis is a group of disorders that includes neurofibromatosis 1 (NF1), neurofibromatosis 2 (NF2), and schwannomatosis. NF1 is the most common of the three with an occurrence of 1/3000. It is an autosomal dominant disorder caused by mutations in the tumor suppressor gene neurofibromin on chromosome 17. Most cases of NF1 occur de novo.

NF2 is an autosomal dominant disorder caused by mutations in the tumor suppressor gene *NF2* on chromosome 22 which encodes the protein Merlin. Like NF1, most cases of NF2 occur de novo. Both NF1 and NF2 are characterized by the growth of tumors throughout the nervous system. NF1 presents during childhood whereas NF2 typically presents in early adulthood. For the purpose of this case, we will focus on NF1.

Tuberous sclerosis

- 2nd most common neurocutaneous disorder
  - 1:6000
- AD; most de novo
- Mutation in *TSC1* or *TSC2* (mTOR pathway)



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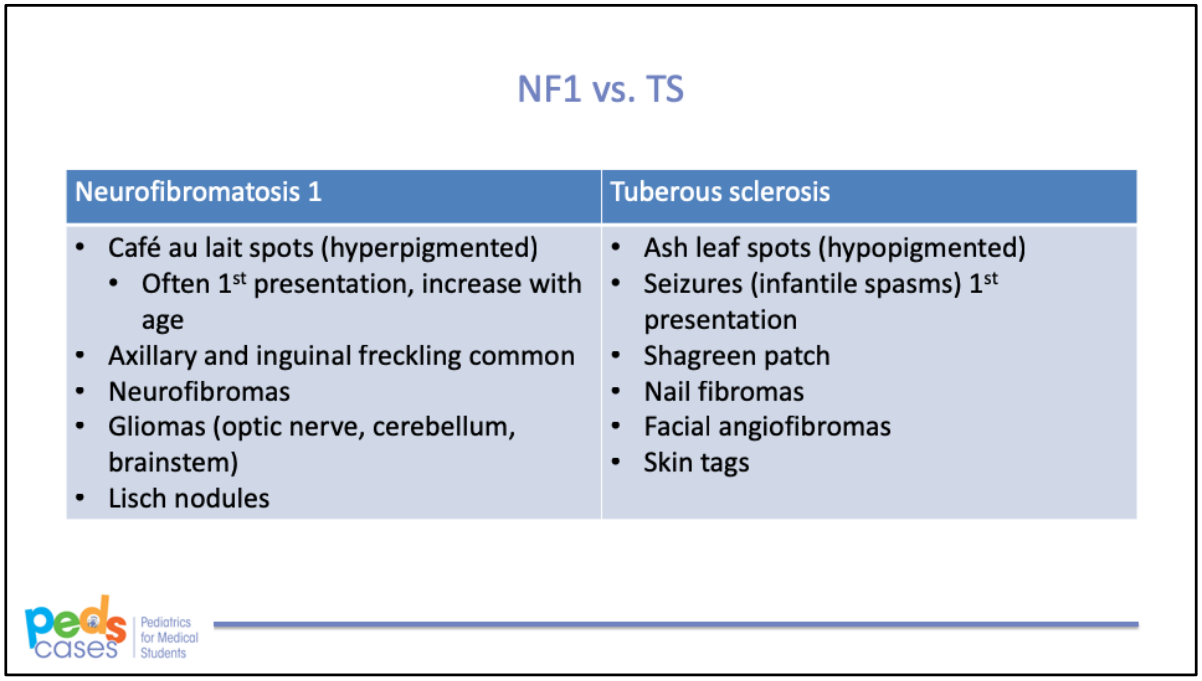
Slide 7: Tuberous sclerosis overview

The second most common neurocutaneous disorder is tuberous sclerosis with an incidence of 1/6000. It is an autosomal dominant disorder caused by mutations in either *TSC1* or *TSC2*, both of which encode tumor suppressors involved in mTOR signaling. Like NF, most cases of tuberous sclerosis occur de novo.

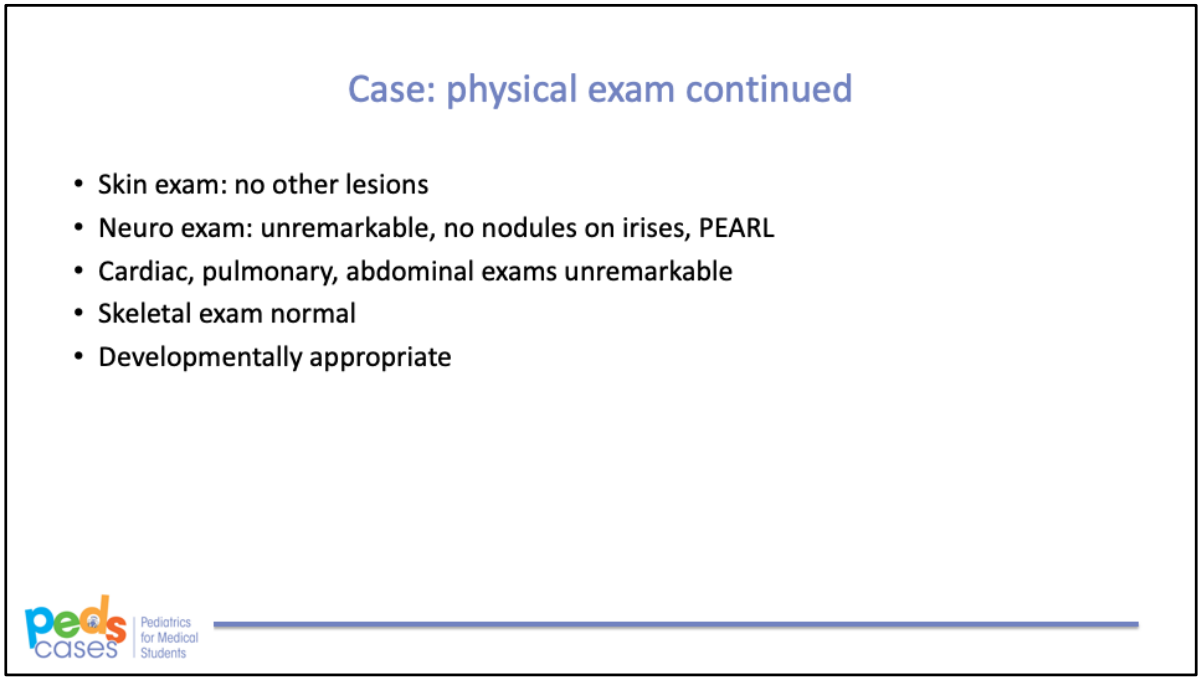
Both NF and TS affect multiple organ systems, and in particular the skin and nervous system. Next we will compare the features and presentation of NF1 and TS.



Slide 8: NF vs TS (table)
As mentioned previously, NF1 and tuberous sclerosis are the two most common neurocutaneous disorders. Let's briefly compare the two disorders. The skin lesions characteristic of NF1 are hyperpigmented macules known as cafe au lait spots. Cafe au lait spots are often the first presentation of NF1 and tend to increase in number throughout childhood. Axillary and inguinal freckling is also common in NF1. In TS, the skin lesions are ash leaf spots which are hypopigmented and polygonal or oval shape. These can be best viewed with a Wood's lamp. Other skin lesions in TS includes Shagreen patches, ungual fibromas, and facial angiofibromas which are pathognomonic but usually appear at a later stage. TS often first presents with seizures including infantile spasms.

NF1 has a variety of neurocutaneous features in addition to the typical skin findings including cutaneous neurofibromas. Gliomas involving the optic nerve might also be seen. In addition, individuals with NF1 have higher risk of other CNS tumors, mainly astrocytomas and brainstem gliomas. The mean age at diagnosis for astrocytomas is 4.5 years and the risk persists into adulthood. Patients with astrocytomas are usually asymptomatic and diagnosed incidentally on brain imaging, but the most frequent presentation is signs and symptoms associated with increased

intracranial pressure. On the other hand, most NF1 patients with brain gliomas are symptomatic. In the eyes the most common findings are Lisch nodules on the iris as well as pallor of the optic disc. Now let's go back to the case.



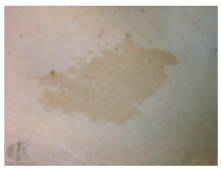
Slide 9: Physical exam

To recap, you were seeing a 6-month-old male infant in community clinic when you noticed some hyperpigmented macules that you think are cafe au lait spots while doing a routine skin inspection. Your preceptor agrees. You are a keen medical student that recently reviewed neurocutaneous disorders, and you suggest a possible diagnosis of NF1. You continue with your complete physical exam. You do not notice any other obvious skin lesions. You move on to a neuro exam. There are no nodules on either iris, both pupils are equal and reactive to light. The rest of the neuro exam is unremarkable. Cardiac, pulmonary, and abdominal exams are unremarkable as well. There are no obvious skeletal abnormalities. The child appears to be developmentally appropriate based on your history and observations. After you are done the physical exam, your preceptor asks if this child meets the diagnostic criteria for NF1.

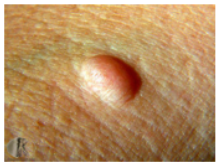
NF1 diagnostic criteria

- At least two of:
  - 6 café au lait spots >5mm in diameter (prepubertal) or >15mm (postpubertal)
  - At least two neurofibromas or one plexiform neurofibroma
  - Freckling in the inguinal or axillary region
  - Optic glioma
  - Two or more lisch nodules
  - Osseous lesions (sphenoid dysplasia, thinning of long bones)
  - First degree relative with NF1

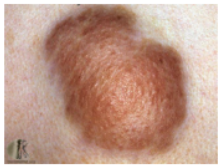
Café au lait spot



Neurofiboma



Plexiform neurofibroma



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Slide 10: NF diagnostic criteria

Although NF1 is a genetic disorder, genetic testing is often not required for diagnosis. Instead, there is a set of criteria that can be used to diagnose NF1 Two or more of the following are required to make the diagnosis:

1) Six or more cafe au lait spots > 0.5 cm in diameter if prepubertal or > 1.5 cm in postpubertal children. Cafe au lait spots are discrete uniformly pigmented macules or patches, varying from light to dark brown with smooth or irregular borders. In general, CALS are more common in African American and HIspanic than in Caucasian. Therefore, in Caucasian children, more than 3 may prompt evaluation.
2) Two or more cutaneous neurofibromas or one plexiform neurofibroma. Plexiform neurofibromas presents as a soft plaque with overlying hyperpigmentation with or without hypertrichosis. It has the potential for malignant transformation which can manifest as tenderness over the leasion. It can involve all skin levels down to bone and viscera. It may cause compression, distortion, or overgrowth of structures.
3) Freckling in the inguinal and/or axillary region.
4) Optic glioma. Optic gliomas are the most common CNS tumor in NF1. They occur in 15% of children younger than 6 years of age with NF1. They rarely occur in older children and adults. The patient can present with headache, visual field defects,

proptosis, strabismus, nausea, anorexia, hypothalamic dysfunction, and precocious puberty.
5) Two or more Lisch nodules on the iris which are hamartomas of the iris. It may require slit-lamp to diagnose but does not affect vision.
6) Osseous lesions including sphenoid dysplasia, and thinning of long bones
7) First degree relative with NF1

If you recall, your patient has only 5 cafe au lait spots that are >5mm in diameter and does not currently meet the diagnostic criteria for NF1. It is important to note that the presentation of NF1 might progress over time. Patients can often first present with only a few cafe au lait spots. Other manifestations of NF1 including freckling, neurofibromas, Lisch nodules or gliomas tend to present later in childhood or after puberty, making it essential to do regular skin exams and follow all patients closely if a neurocutaneous disorder is suspected.

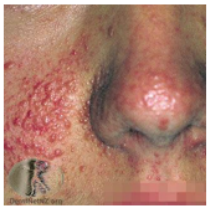
Tuberous Sclerosis: major criteria

Major criteria: need ≥2 major OR 1 major + 2 minor

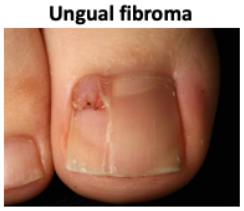
- ≥3 ash leaf spots >5mm in diameter
- ≥3 angiofibromas or 1 fibrous cephalic plaque
- ≥2 ungual fibromas
- Shagreen patch
- Multiple retinal hamartomas
- Cortical dysplasia (tubers)
- Subependymal nodules
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma
- Lymphangioleiomyomatosis
- ≥2 angiomyolipomas

Ash leaf spots

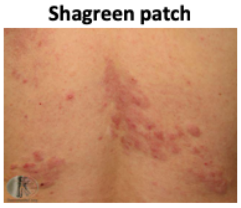
Angiofirbomas



Ungual fibroma



Shagreen patch



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Slide 11: major criteria

After reviewing NF1 presentation and diagnosis with your preceptor, they ask you if you know what the other most common neurocutaneous disorder is. You know that it is tuberous sclerosis but can't quite remember the long list of diagnostic criteria. Let's review that now.

There are both major features and minor features. To make a definitive diagnosis, you need two major features or one major with at least two minor features. A definitive diagnosis can also be made through genetic testing. For possible diagnosis, you need one major feature or at least two minor features.

The major features are:

1) At least 3 hypomelanotic macules with > 5 mm diameter, known as ash leaf spots
2) 3 or more angiofibromas or one fibrous cephalic plaque
3) 2 or more ungual fibromas
4) Shagreen patch. Shagreen patches are a connective tissue nevus that is skin colored and occurs on back and buttocks
5) Multiple retinal hamartomas. Hamartomas are abnormal growths of tissue.
6) Cortical dysplasia including tubers
7) Subependymal nodules

8) Subependymal giant cell astrocytoma
9) Cardiac rhabdomyoma
10) Lymphangioleiomyomatosis (LAM)
11) 2 or more angiomyolipomas
Please note that a definitive diagnosis cannot be made if the only two major criteria present are lymphangioleiomyomatosis and angiomyolipomas.

The minor features are:
1) Confetti skin lesions
2) At least 3 dental enamel pits
3) At least 2 intraoral fibromas
4) Retinal achromic patch
5) Multiple renal cysts
6) Nonrenal hamartomas

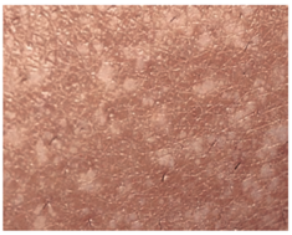
Please refer to the pedscase on tuberous sclerosis for more information including a clinical case.

Tuberous Sclerosis: minor criteria

Minor criteria: need 1 major + 2 minor

- Confetti skin lesions
- ≥3 dental enamel pits
- ≥2 intraoral fibromas
- Retinal achromic patch
- Multiple renal cysts
- Nonrenal hamartomas

Confetti skin lesions



Bolognia et al. (2014)

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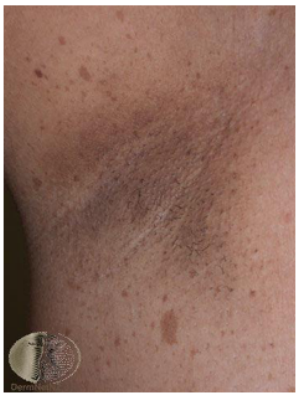
Slide 12: minor criteria
The minor features are:
1) Confetti skin lesions
2) At least 3 dental enamel pits
3) At least 2 intraoral fibromas
4) Retinal achromic patch
5) Multiple renal cysts
6) Nonrenal hamartomas

Please refer to the PedsCases on tuberous sclerosis for more information including a clinical case.

Case: follow up

- 3 year old male
  - No concerns
  - Developmentally appropriate
  - IUTD
  - 11 café au lait (6-15mm)
  - Axillary freckling
  - No neurofibromas, no visible plexiform neurofibromas
  - Skeletal exam normal
- Yearly eye exams arranged
  - Last exam normal



https://www.dermnetnz.org/topics/neurofibromatosis/

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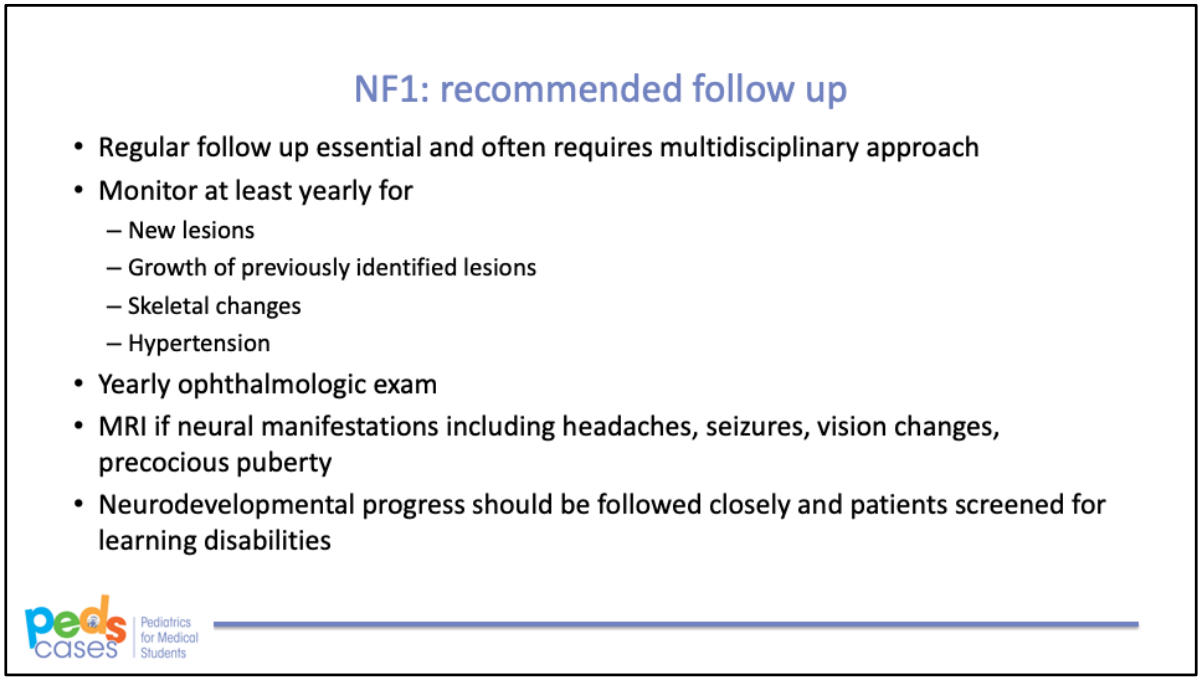
Slide 13: follow up

You are back in the same community clinic as a new resident during your pediatrics rotation. You are asked to see a 3-year-old male for a well child check and are told to pay close attention to the skin exam. You notice the name looks familiar, and you realize it's the same patient you saw in clinic a few years ago. Over the last few years, there has been no concerns. He is on track for his development. His immunizations are up to date and his growth is tracking appropriately. You begin your exam starting with the skin exam. You notice 11 cafe au lait spots that range from 0.6 cm to 1.5 cm in diameter. You also notice that his axillae has some freckling. There are no neurofibromas and no visible plexiform neurofibromas. Since this patient was suspected of having NF1, he was sent for yearly eye exams as a precaution. His eye exam a month ago was normal. Skeletal exam is normal with no bony abnormalities. As the number of cafe au lait spots has increased and this patient now has axillary freckling, you are able to diagnose him with NFI. His parents were already counselled on what NF1 is when he initially presented for his well child check over 2 years ago but as it was not clinically confirmed you had a teaching session with them now that is became relevant. You reviewed the different terms, the necessity for multidisciplinary involvement and reiterated the importance of regular follow up appointments.



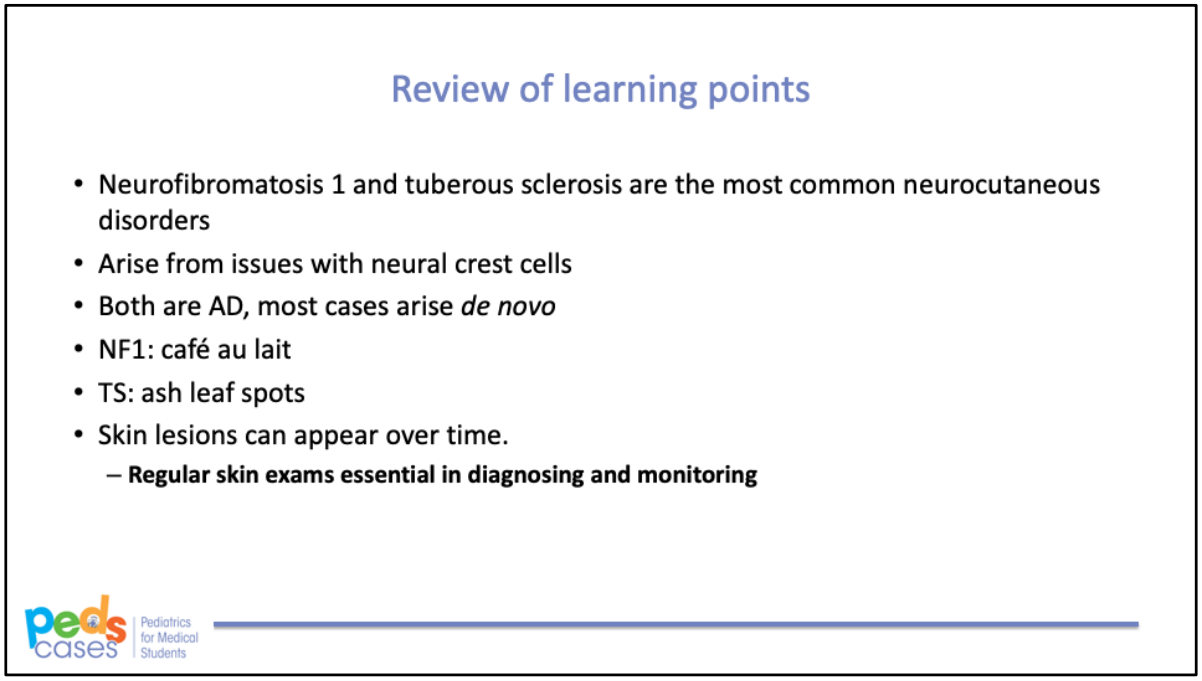
Slide 14: following a patient with NF1

Children with NF1 need to be closely followed for further manifestations of NF1. As NF1 tends to progress throughout childhood and adolescence, children need to be frequently reassessed at least yearly for new skin lesions, growth of previously identified lesions, skeletal changes, and hypertension. In addition, children with NF1 should undergo a yearly ophthalmologic exam to assess for vision changes. There is controversy around the need for MRI screening for brain tumors and lesions in the optic chiasm. Given the fact that MRI could pick up nonspecific or questionable findings leading to more invasive testing or anxiety among family members, routine screening MRIs are not recommended as per current guidelines. However, children with NF1 should be sent for MRI if any neural manifestations arise including headaches, seizures, vision changes, and precocious puberty. In addition, there should be a clear discussion between families and physicians regarding the risks and benefits before the imaging studies.

Most children with NF1 will have normal and typical development and cognition; however, up to 8% of children with NF1 can exhibit learning difficulties and varying degrees of intellectual disability, making it essential to follow the neurodevelopmental progress and screen for learning disabilities, especially in the

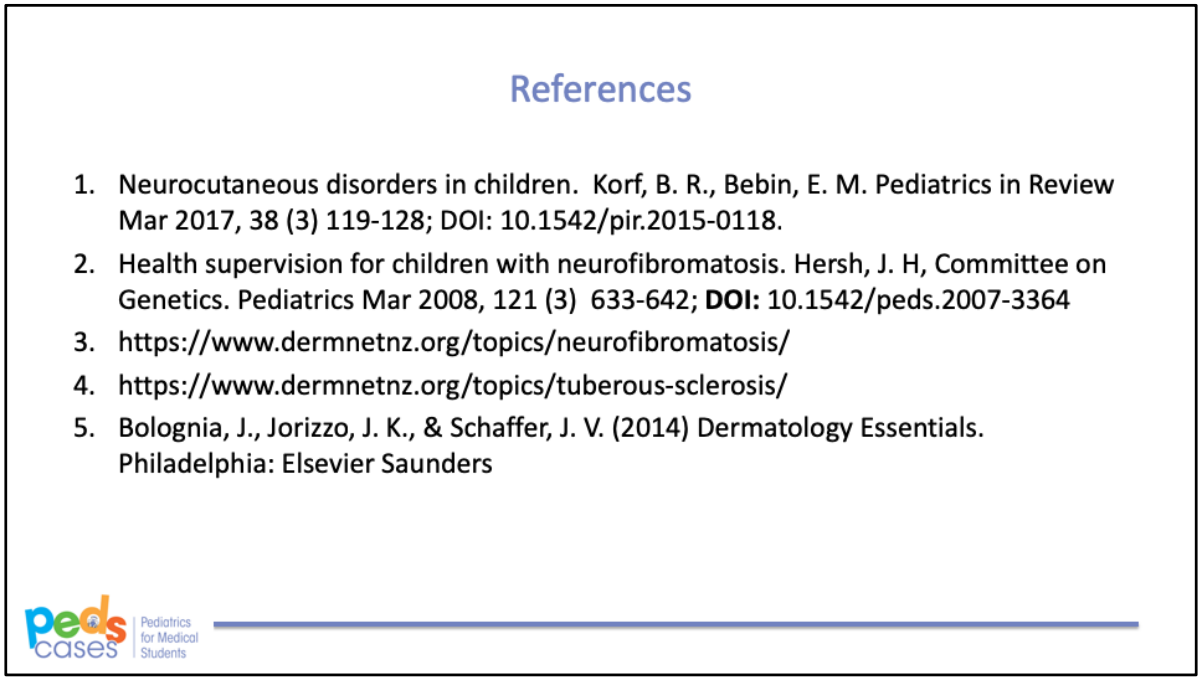
realm of math skills.

Managing a patient with NF1 often requires a multidisciplinary approach that can involve multiple medical specialists in addition to allied health care professionals. More specifically, all patients will need a family doctor or pediatrician for regular follow up as well as an ophthalmologist. In addition, children with previous history of seizures most likely will need to be assessed regularly by a neurologist. The overall care of a child with NF1 or other neurocutaneous disorders could be very complex, and the key to comprehensive care is to ensure effective communication among healthcare professionals along with community partners including teachers and other caregivers.



Slide 15: Review of learning points

Today we reviewed the two most common neurocutaneous disorders, NF1 and TS. Both disorders are autosomal dominant, with most cases occurring de novo. NF1 and TS present with characteristic skin lesions with NF1 presenting with hyperpigmented cafe au lait spots and TS presenting with hypopigmented ash leaf spots. Neurocutaneous disorders have a wide range of presentation with all affecting the skin and nervous system as well as other systems. As mentioned in the case, patients may not meet diagnostic criteria for a neurocutaneous disease at initial presentation. This makes regular follow up and monitoring essential to make a diagnosis as early as possible.



Slide 16: References

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