Activity Overview

This presentation serves as a brief overview of the pathophysiology of Neurofibromatosis type 1, a common genetic disorder associated with neurocutaneous abnormalities, as well as its impact on the health of adult patients with this diagnosis. A review of the literature regarding the care of adult patients was conducted; the information is presented as a primer for providers caring for these patients in the community to guide management, screening, and surveillance and improve the delivery of care to this population.

Target Audience

This activity is intended for primary care physicians neurologists, neurosurgeons, and oncologists.

Instructions to Receive Credit

To receive credit, read the introductory CME material, watch the webcast, and complete the evaluation, attestation, and post-test, answering at least 70% of the post-test questions correctly.
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Medical Surveillance and Screening in Adults with Neurofibromatosis Type 1

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Disclosure Statement

The content of this activity has been peer reviewed and has been approved for compliance. The faculty and contributors have indicated the following financial relationships, which have been resolved through an established COI resolution process, and have stated that these reported relationships will not have any impact on their ability to give an unbiased presentation.

Lindsay Lipinski, MD, has indicated no real or apparent conflicts. The peer reviewers and activity planners have no financial relationships to disclose.
Learning Objectives

Upon completion, participants should be able to:

• Understand the current care system for patients with NF1 and the potential barriers to accessing care in the adult population

• Understand the basic pathophysiology of NF1, and recognize that the health issues that affect children with NF1 are often different from those that affect adults

• Become familiar with NF1-related conditions that affect adults, and the impact the diagnosis has on overall wellbeing

• Understand the role of surveillance and screening in adult patients with NF1, and be able to identify when imaging or subspecialty referral is appropriate
Outline

• Brief overview of NF1
• Background- why is it important to talk about adults?
• System-based review of NF1-related health issues
• Multidisciplinary care
• Summary/clinical pearls
Neurofibromatosis Overview

- Autosomal dominant mode of inheritance (50% new mutations) with nearly 100% penetrance by age 5.
- The NF1 gene on chromosome 17q11.2 encodes the large tumor suppressor gene, neurofibromin.
- Wide inter- and intra-familial phenotypic variability (weak genotype-phenotype correlation).
- Occurs without regard to sex, race, or ethnic background.
Neurofibromatosis Overview

- NF1 is a multisystem disorder presenting with both benign and malignant tumors, dermatologic findings, and developmental and functional issues.
- Cutaneous neurofibromas are the hallmark and almost all adult patients have them.
- CNS tumors are most common (~20% of this population will have one), though other tumors have a higher incidence as well.
Neurofibromatosis Overview

**NIH Diagnostic Criteria for neurofibromatosis type 1**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
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<tbody>
<tr>
<td>Six or more café-au-lait macules of more than 5 mm in greatest diameter in prepubertal individuals, and more than 15 mm in greatest diameter in postpubertal individuals</td>
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<td>Two or more neurofibromas of any type or one plexiform neurofibroma</td>
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<td>Freckling in the axillary or inguinal regions</td>
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<td>Optic glioma</td>
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<td>Two or more iris hamartoma (Lisch nodules)</td>
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<td>Distinctive bony lesion, such as sphenoid dysplasia, or medullary narrowing and cortical thickening of the long bone cortex with or without pseudoarthrosis</td>
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<td>A first-degree relative (parent, sibling, or offspring) with NF1 based on the above criteria</td>
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(NIH consensus statement, 1988)
Background

• Initial diagnosis is almost always established by age 8 (DeBella, Szudek et al. 2000).

• While the number of NF specialty clinics nationally is increasing, many are focused on the care of pediatric patients or are financially or geographically limiting (Merker, Dai et al. 2018).
  – Primary care providers and specialists in the community are often the first and only resource for many patients.

• No clear consensus exist for the general medical management of adult patients, and the NF-related conditions the arise in adulthood may go overlooked or may be underappreciated.
  – ACMG Practice Guideline 2018 a great start!
In NF1, adults are not “big children.”

The general belief is that the overall severity of the disease increases with age, but in reality:
- Cutaneous findings do increase with age, but...
- Aggressive features, if they occur, most commonly happen during childhood with relative stability in adulthood*

Some risks are lifelong

Early recognition and treatment of the “adult-specific” NF-related health issues has the potential to save lives and preserve quality of life.
General

- The goal for patients and clinicians alike is “informed vigilance.” (Korf and Rubenstein 2005)

- Life expectancy
  - Overall **decreased by 8-15 years** (Zoller, Rembeck et al. (Evans, O'Hara et al. 2011)
  - BUT, early deaths due to malignancy or complications related to surgery shift the curve, and most adults with NF1 can expect a **normal lifespan**
  - More commonly die from the same causes as in the non-NF1 population (Uusitalo, Leppavirta et al. 2015)
Dermatologic

• Café au lait spots
  – Benign; usually present by age 1-2 years but their number declines after age 50

• Cutaneous and subcutaneous neurofibromas
  – Develop at adolescence and increase in number over lifespan
  – May be painful or disfiguring
    • Referral to plastic surgery should be considered for pain or potentially cosmesis
Cardiovascular

- **Annual screening for hypertension**
  - Essential hypertension most common
  - NF-related causes:
    - Renal artery stenosis
      - In adults <30 years of age who do not respond to first line medication management, or who have abdominal bruits, consider vascular imaging. (Duan, Feng et al. 2014)
    - Pheochromocytoma
      - In young adults or if HTN is episodic and/or vasomotor sx (sweating, headache, palpitations), consider testing for plasma metanephrines. (Erem, Onder Ersoz et al. 2007)

- **Vasculopathy**
  - Frequently asymptomatic and not fully characterized (Friedman, Arbiser et al. 2002)
Neurologic

• Seizure
  – Epilepsy risk is lifelong
  – More commonly related to a mass lesion, but can also be idiopathic
  – Treatment as in non-NF1 population

• Hydrocephalus
  – More likely to be asymptomatic ventriculomegaly
  – Can also develop due to mass lesion or aqueductal stenosis

• Stroke risk modestly elevated (Terry, Jordan et al. 2016)
  – Related to cerebrovascular vasculopathy
Neurologic

• Plexiform neurofibromas
  – Diffuse: develop during childhood, rare after puberty
  – Nodular: more likely to become painful

(Mayoclinic.org)
Neurologic

• Brain tumors
  – Optic pathway gliomas
    • Typically quiesce after age 6 (Listernick, Louis, Packer, & Gutmann, 1997), and adult patients typically do not experience decrease in visual function (Creange et al., 1999).
    • History of visual symptoms at least annually and full ophthalmologic exam q1-2 years (Beres 2018).
    • Repetitive imaging not recommended
  – Lifelong risk for gliomas, meningiomas
Neurologic

• Malignant Peripheral Nerve Sheath Tumor
  – Occur in 2-5% of patients with NF1 (Ducatman, Scheithauer et al. 1986), all ages
  – Most often arise from pre-existing plexiform neurofibromas
  – Symptoms: increase in volume of previously known neurofibroma, increased pain, and/or motor deficit
  – Treatment regimens vary widely, prognosis remains poor with 20-50% 5 year survival (Stucky, Johnson et al. 2012) (Baehring, Betensky et al. 2003)
  – If clinical concern arises, early referral to cancer center is indicated
Orthopedic

• Scoliosis
  – Usually present in late childhood or early adolescence
  – May be a persistent cause of pain or neurologic dysfunction
  – Annual clinical evaluation should be performed
  – If present, curve progression should be monitored by a spine surgeon.

• Osteoporosis
  – Higher prevalence and occurs at an earlier age
  – Workup and treatment as in non-NF1 population
Pain

• Headache
  – Overall incidence is probably similar to general population (Creange et al., 1999)
  – Migraine incidence may be increased

• Non-headache pain
  – Etiologies include subcutaneous, plexiform, peripheral nerve or root neurofibroma, or malignant peripheral nerve sheath tumor (Creange et al., 1999)
    • Can be radicular pain, distribution of a specific nerve, cutaneous, or truncal
  – Degenerative spinal abnormalities (related to paraspinal NF) may be a cause of pain
Pain

- Optimal pain management may include multiple modalities (pharmacologic and nonpharmacologic)
  - Analgesics, antidepressants, anticonvulsants, opioids, etc.
  - Intrathecal delivery, neurostimulation

- Referral to a pain management specialist should be considered if first line therapies fail
Psychological

- Significant psychosocial burden:
  - Unpredictable nature of disease
  - Repetitive medical appointments/procedures
  - Stigmatization due to cosmetic features of the condition & body image issues

- Anxiety, depression, social withdrawal, behavioral problems
- Incidence of psychiatric comorbidity (most commonly depression) at least twice as high as the general population (Cohen, Levy et al. 2015)
- Screening for depression should be part of standard care.
Psychological

• Learning disabilities/ADHD/attention impairment (Descheemaeker, Plasschaert et al. 2013)

• Nonspecific cognitive impairment (Descheemaeker, Plasschaert et al. 2013)
  – May correlate with underlying CNS involvement
  – Most patients have normal intelligence

• Data limited; recognize this may effect employability and schooling.
Non-CNS Malignancy

• Most studies show a modest but elevated risk of other malignancies in NF1 patients
  – Breast cancer in women
    • Earlier onset and poorer survival (Uusitalo, Kallionpaa et al. 2017)
    • Start screening with mammogram at age 30 (NCCN guidelines)
  – Gastrointestinal cancers, thyroid cancers (Uusitalo, Rantanen et al. 2016)
Non-CNS Malignancy

- Some advocate for a single whole-body MRI at transition to adulthood (Evans, Salvador et al. 2017), with patient education and encouragement to report any concerning signs or symptoms.

- Some experts argue that routine screening with PET and/or MRI may be warranted, as survival may be related to tumor volume at diagnosis (Porter, Prasad et al. 2009).
  - If utilized, should be done through a cancer or subspecialty center for interpretation and clinical application
## Cancer risk

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Lifetime Risk</th>
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<tbody>
<tr>
<td>Glioma of the optic pathway</td>
<td>15–20%</td>
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<tr>
<td>Other brain tumour</td>
<td>More than fivefold increase</td>
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<tr>
<td>Malignant peripheral nerve-sheath tumour</td>
<td>8–13%</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumour</td>
<td>4–25%</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>About fivefold increase</td>
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<tr>
<td>Leukaemia</td>
<td>About sevenfold increase</td>
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<tr>
<td>Phaeochromocytoma</td>
<td>0.1–5.7%</td>
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<tr>
<td>Duodenal carcinoid tumour</td>
<td>1%</td>
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<tr>
<td>Rhabdomyosarcoma</td>
<td>1.4–6%</td>
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</tbody>
</table>

*Table: Lifetime risk of different tumours in children and adults with neurofibromatosis type 1*  

(Hirbe and Gutmann 2014)
Genetics

• Consider referral to geneticist/genetic counselor for:
  – Adults of reproductive age who desire genetic counseling for family planning
  – Guidance during pregnancy
  – Unclear diagnoses/NF variants
Other

• Pregnant women with NF1
  – Pregnancy associated with increased risk of maternal morbidity (Terry, Barker et al. 2013)
  – Consider referral to a high risk obstetrician
  – Neuro imaging usually not necessary for labor/delivery

• Vitamin D testing/supplementation? (Petramala, Giustini et al. 2012)
Multidisciplinary Approach to Care

• A Comprehensive NF Clinic may offer patients additional resources, simplify multi-specialty care, provide family support, offer clinical trials and novel treatments.

• Should work in conjunction with primary care provider.
### Features of neurofibromatosis type 1 as a function of the age when they may first be apparent

**Birth through age 2**
- Café-au-lait spots, pseudoarthrosis, sphenoid wing dysplasia, optic pathway gliomas, plexiform neurofibromas (rarely)

**Ages 2 through 6**
- Axillary freckling, Lisch nodules, optic pathway gliomas, other CNS tumors, learning disabilities or speech delay, plexiform neurofibromas

**6 to 10 years**
- Learning disabilities, attention deficit disorders, scoliosis, plexiform neurofibromas, increased risk of other cancer types (e.g., rhabdomyosarcomas), headaches

**Adolescence**
- Subcutaneous and cutaneous neurofibromas, malignant transformation of pre-existing plexiform neurofibromas, isolated MPNST, hypertension

**Adulthood**
- Increasing number of cutaneous and subcutaneous neurofibromas, MPNST, hypertension

CNS: central nervous system; MPNST: malignant peripheral nerve sheath tumors.

Summary

Key points for providers involved in the care of patients with NF1 in the community
Summary-1

• Important to consider NF1-related conditions, BUT common things remain common...
  – Expect adult patients with NF1 to have a normal lifespan, and therefore will develop conditions associated with aging in the general population
Summary-2

• Malignant peripheral nerve sheath tumors are the most common life-threatening NF-related condition in adults with NF1.
  – But there is no screening...
  – Worry if: increase in size of a known PN, increased or persistent pain, neurologic symptoms
  – Refer to a subspecialty center early
Summary-3

• **Chronic pain** complications predominate in adulthood and have the biggest impact on daily living.
  – Don’t overlook pain complaints and seek specialty care if needed
Summary-4

• Remember to pay attention to **blood pressure** and encourage annual **ophthalmology exams**.
Summary-5

• Use neuro-imaging sparingly and specifically
  – While no consensus, general guideline is to **only image in the setting of symptoms.**
  – MRI>CT to avoid radiation
Summary-6

• Screen for and recognize depression symptoms, and treat as in non-NF1 population.

• Recognize intellectual disabilities or learning disorders may impact psychosocial function.
Summary-7

• Have a high index of suspicion for other malignancies
  – Early screening for breast cancer in women
Summary-8

- Referral to a **multidisciplinary care center** if geographically and financially feasible for the patient.
Thank you!
References


References


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