Pain, Fatigue, Common Musculoskeletal Issues in Neurofibromatosis 1

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Pediatric Rehabilitation Medicine Attending

2024 NF Family Day

Children's National

CHILDREN'S TUMOR FOUNDATION
NF ENDURANCE

Objectives

To understand common pain etiologies in patients with Neurofibromatosis (NF)

Know what to consider for treatment

Recognize common musculoskeletal changes seen and its impact in function, complications

Understand Physical Medicine and Rehabilitation (PMR) treatment approach

Know when to ask to get an evaluation done by PMR

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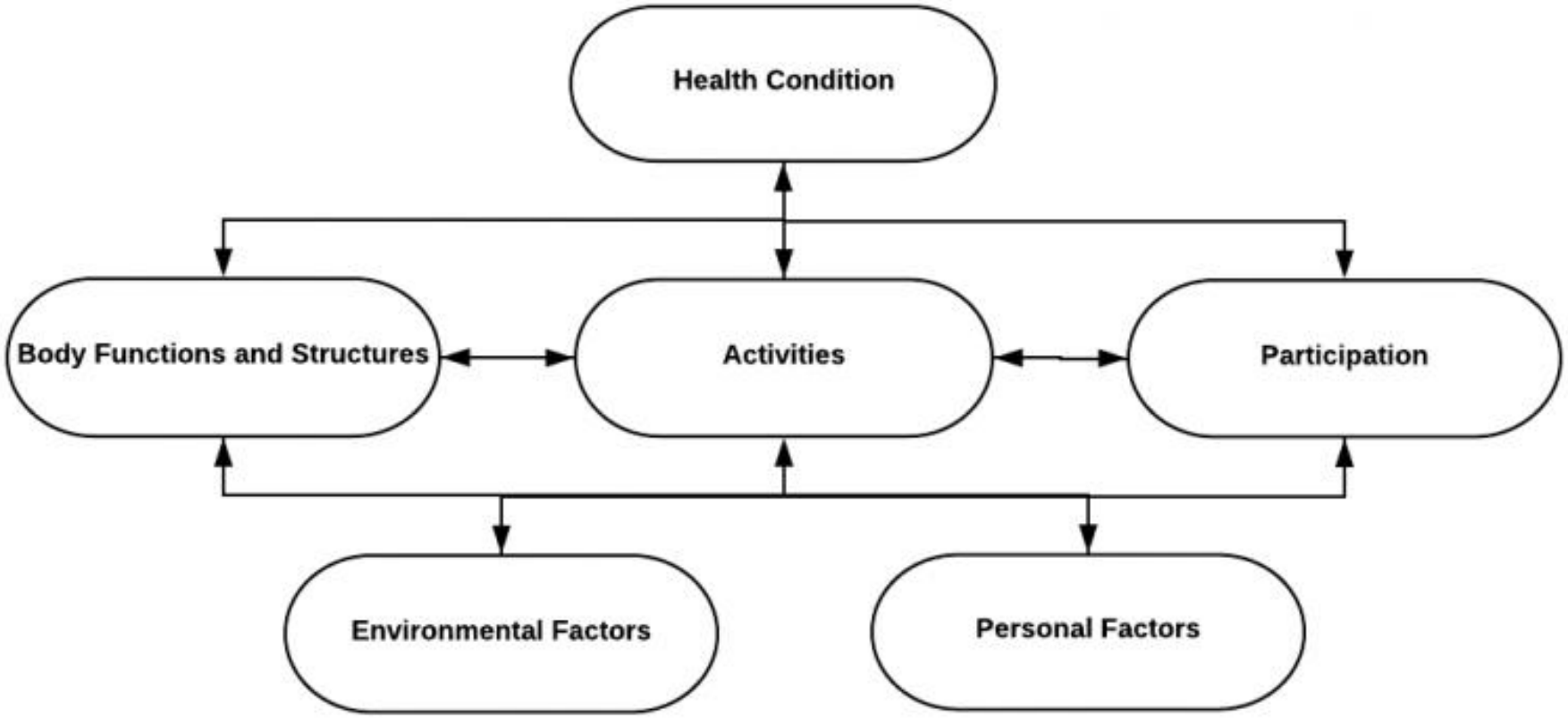
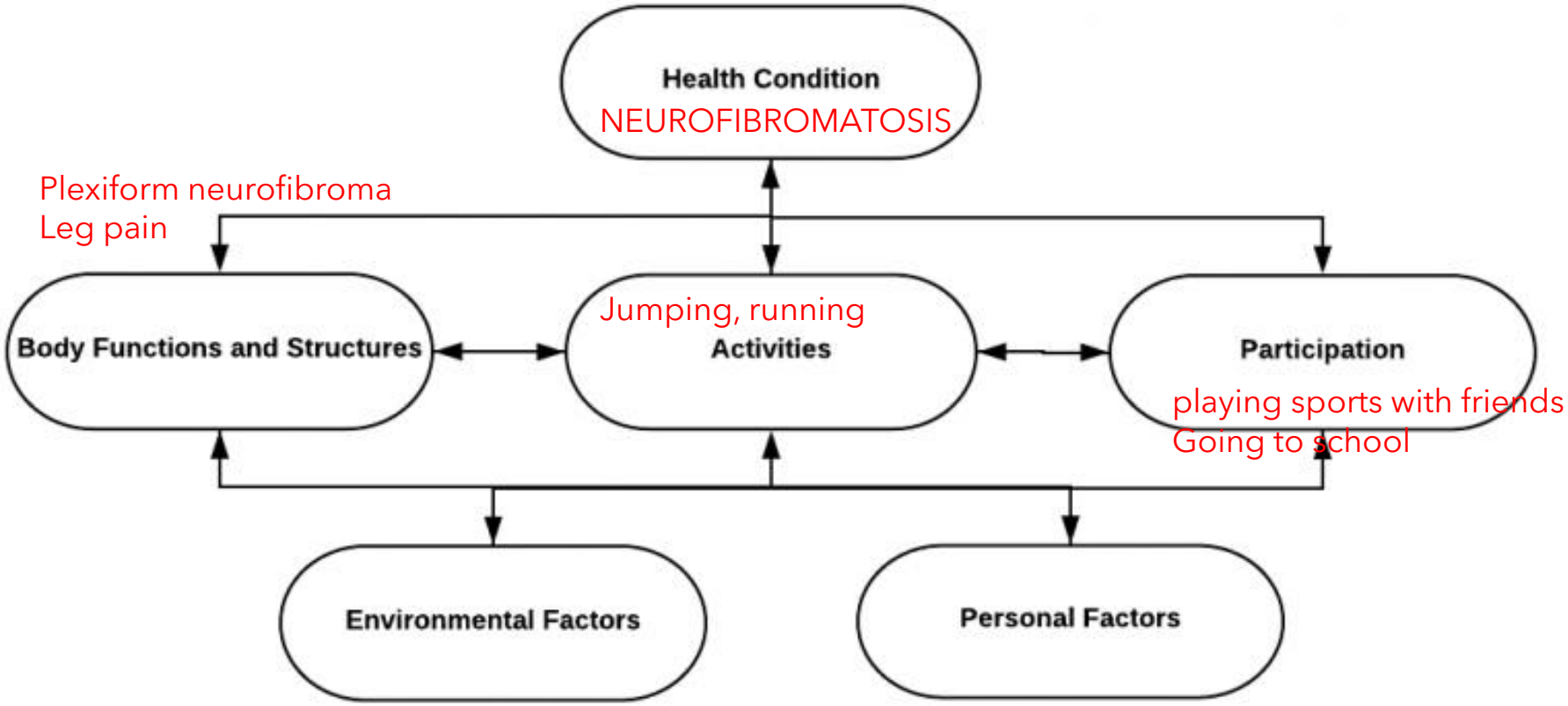
- The International Classification of Functioning, Disability and Health



- The International Classification of Functioning, Disability and Health



Epidemiology of Pain - Incidence

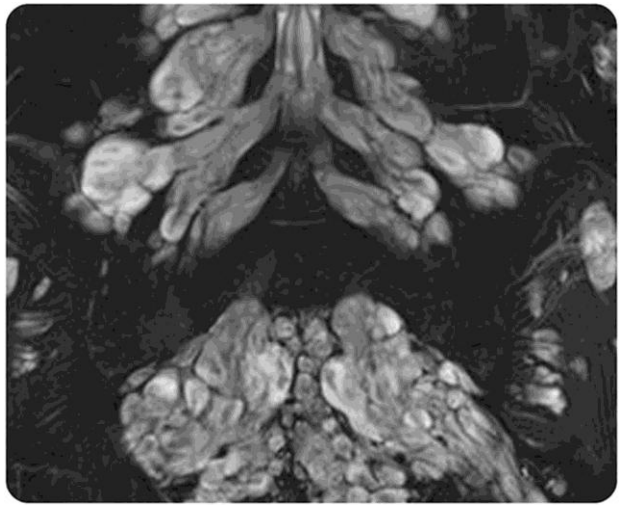
- At least 50%[1] to 65%[2] who has plexiform neurofibromatosis reported having pain
- 95& with pain during lifetime, average having pain for 11.2 yr
- Could be multiple body parts

- Depending on the size (larger tends to be more symptomatic)
- Location (sensitive areas such as tumor at head/neck) tends to have more symptoms, m/c in limbs
- Perhaps diffuse and infiltrating tumors tends to have more pain, number of tumors
- Moderate pain, affecting sleep

[1]Nguyen, R. et al
[2]Yang, Siaoqin et al. 2022

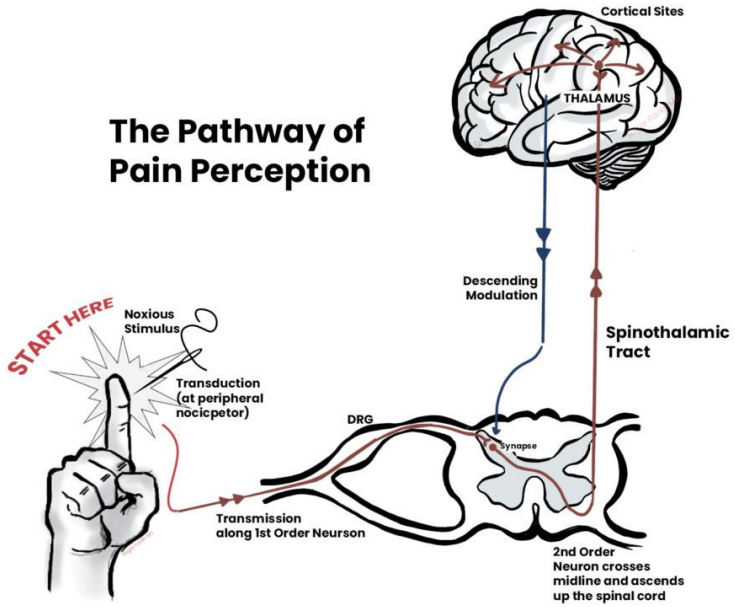
Why Increased Pain?

- Changes in pain pathway
- Compression of spinal nerve roots causing radiculopathy
- Spinal deformities causing restrictive motion, and secondary musculoskeletal pain
- Muscle imbalances and postural asymmetries



Grimsrud,K et al. 2017

Why Increased Pain?



- Neuronal hyperexcitability in the setting of reduced neurofibromin
- Perhaps there's changes in nociceptive sensory neurons that explains increased pain perception
- A subset of small-diameter dorsal root ganglion neurons has increased excitability
- Pain signaling changes may be happening through increase in basal and cytokine stimulated RAS GTO elevation

Impact of living with Plexiform Neurofibromas related Pain?

- 59-86% report pain interfering with function
- Decreased quality of life
- Difficulties with motor function
- Psychologic impact – depression, anxiety
- Interference with cognition, dysfunction in high-level processing
- Adult- chronic pain, opioid dependence
- Males with worse pain interference, mobility, function, stigma, meaning/purpose
- Females with upper extremity function interference

What can we do for pain?

Depending on location, and reason/ type of pain

Treatment of Plexiform Neurofibroma – pharmacologic, surgical treatment

Symptomatic Treatment with Medication

Acetaminophen/ NSAIDS

Gabapentin

Clonidine

Lidocaine patch

Opioids?

Therapeutic exercises:

OT/PT, desensitization

Complementary treatment

Yoga, meditation

Trigger point injection / dry needling, exercise, acupuncture, counseling,

Acetaminophen/ NSAIDS

- Acetaminophen (Tylenol)
  - Reduces COX pathway activation by inhibiting the synthesis of prostaglandin
  - Side effect: Liver failure
  - Pills, tablets, liquids (160mg/5ml), rectal suppository

- Nonsteroidal Anti-Inflammatory Drugs, NSAIDS
  - Inhibit COX enzyme
  - Side effect: gastro-intestinal upset, ulcer, kidney damage
  - Tablets, pills, liquid (100mg/5ml)

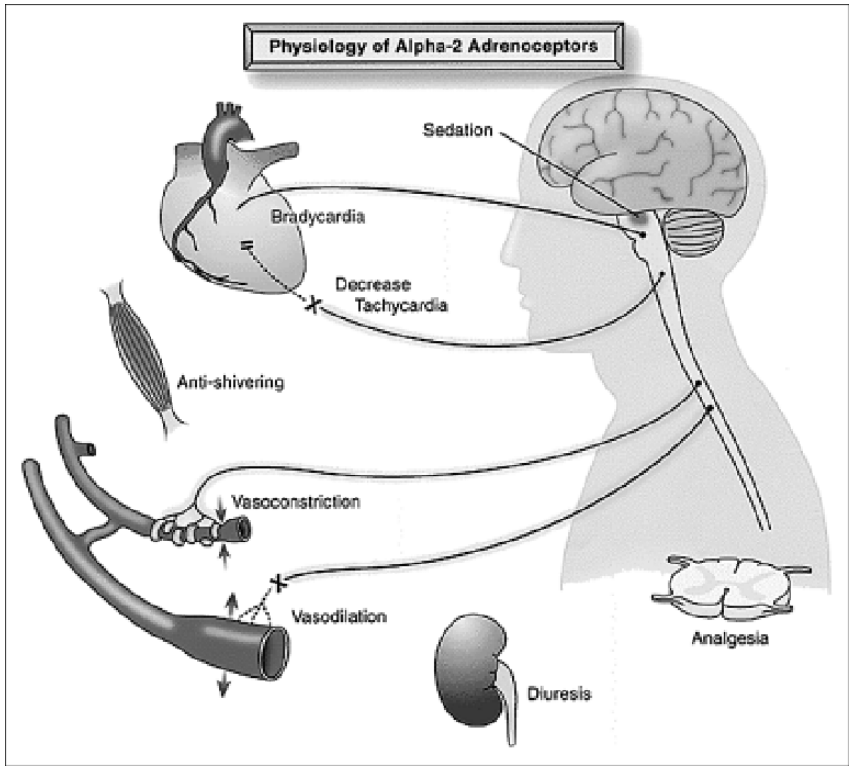
Gabapentin (Neurontin)/ Pregabalin (Lyrica)

- Inhibits action of alpha subunits, Reduces the release of monoamine neurotransmitters (excitatory neurotransmitters)

- Side effects
  - Sleepiness, feeling tired, dizziness
  - Upset stomach
  - Less common: weight gain, swelling, allergic reaction, blurry vision, difficulties thinking, behavioral changes

- Comes in capsules, tablets, liquids

Clonidine



- Stimulation of alpha-2-receptors in the dorsal horn reduces pain transmission (noradrenaline) central and peripheral sympathetic nerve terminals
- Side effects:
  - hypotension, bradycardia, dizziness, sleepiness, constipation, dry mouth, calmness
- Tablets, liquid, patch

Kamibayashi T, Maze M. Clinical uses of alpha 2-adrenergic agonists. Anesthesiology 2000;93:1345-1349

Lidocaine patch

- Reduces sodium ion influxes, inhibit action potential and decrease nerve impulse conduction
- Side effect:
  - skin irritation, allergic reaction, flushed skin
  - If systematically absorbed; dizziness, sleepiness, nausea vomiting, metallic taste, blurry vision
- 12 hours on / 12 hours off

Other Aches and Pains?

- Musculoskeletal pain ?
- Combination of weakness, hypotonia, fatigue
- Focal musculoskeletal pain
  - Leg pain associated with exercise
  - Feet pain associated with foot misalignment
  - Shoulder/back pain due to overuse
  - Hand pain with writing/drawing
- Nerve pain characteristics are typically sharp, burning versus musculoskeletal pain tends to be more ache

- …but due to multiple reasons, clarifying how this feels may be difficult

Treatment Approach

- Treatment will depend on location, severity, and impact of function including sleep
- Pain coping mechanisms – relaxations, distraction, intermittent simple analgesia use, modification of activities
- Therapeutic Exercises – Physical Therapy/ Occupational Therapy
- Orthotics considerations
- Other Pharmacologic Treatment

Fatigue in NF

Tired, having muscle pain/fatigue after a physical activity, what can we do?

Epidemiology of Fatigue

75% with fatigue in adults

Higher fatigue – cognitive, physical, and rest compared to those without NF cohort

Higher severe fatigue

Cause for fatigue

ENDOCRINE ISSUES – RELATION WITH VITAMIN D DEFICIENCY (28%), OBESITY (18%), HYPOTHYROIDISM (8%)

SLEEP IMPAIRMENT?

MUSCLE DYSFUNCTION

ROSENBERG, A. ET AL. 2023;

In-depth about muscles..

- Reduce strength – grip strength, proximal strength (by 3-43% less)
- Reduced dynamic muscle function – reduced jumping power
- Reduced tone, coordination
- Low strength and agility
- RAS-MAPK pathway interfering with muscle dysfunction
- Reduced muscle cross-sectional area
- Changes in structure – muscle fibrosis, intramyocellular lipid

Treatment Options

- Endocrine appropriate treatment if found
- Muscle strengthening
- Carnitine supplement
  - A 12-week Phase 2a trial :1000 mg daily oral levocarnitine tartrate supplementation between 8-12 with increase in ankle strength, long jump, 6MWT
- ? Whole body vibration therapy

Other common musculoskeletal issues

Hypotonia, Scoliosis

Definition of Low Tone

Figure 1: A child with NF sitting, low tone with poor trunk control. Picture credit from: https://www.candgnews.com/index.php/news/spreading-neurofibromatosis-awareness-108069

- Medical term is called "hypotonia"
- Described typically as having a 'floppy child'

- Clinically can manifest as
- Sitting with 'poor posture'
  - "W" sitting
  - Hypermobile joints
  - Floppy child when picked up
  - "rolling" ankles

Clinical Implications/Impact

- Can affect development (i.e. difficulties sitting on time)
- Can impact/ be associated with secondary musculoskeletal changes such as…
  - Flat feet
  - Pronation (rolling) of feet
  - Scoliosis
- And ultimately cause pain

Treatment Options

- Treatment depends on the severity, involved body parts, its functional impact
- If low tone at trunk, your provider may consider trunk brace/vests

https://www.bostonoandp.com/blog/finding-a-path-to-independence-with-dmo-supergirl-suit/

If hypotonia is affecting ankle/foot

- Depends on whether there's any symptoms (i.e. pain), severity, rigidity, secondary changes

- "supportive shoes" with higher top
- or consider shoe inserts or ankle braces

- Shoe insert for flat feet
- SMO : Supramalleolar orthoses

HotDog - PAIRS

PattiBob - PAIRS

Chipmunk - PAIRS

https://surestep.net/products/surestep-smo/

https://www.cascadeshop.com/shoeinserts.aspx

Ford, Samuel E., MD; Scannell, Brian P., MD. Published September 1, 2017. Volume 22, Issue 3

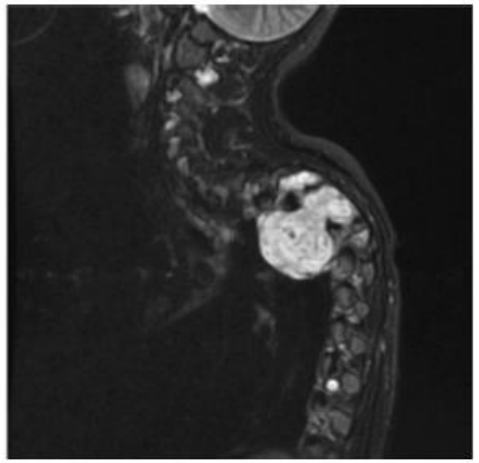
Scoliosis in NF-1

- Most common skeletal manifestation
- About 10% of children with NF have scoliosis
- 2% of pediatric scoliosis is due to NF1
- Most common in (R) thoracic region

- Definition of scoliosis: spine curvature more than 10 degrees
- 2% has neurofibromatosis
  - Can be non-dystrophic
    - More common
  - Or dystrophic (with skeletal dysplasia)
-

Tsirikos, A. et al. Eur. Spine 2005

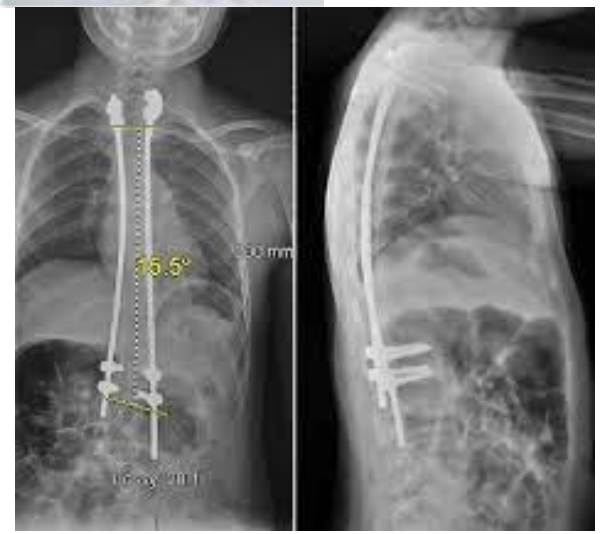
A few distinctive skeletal manifestations



- Sphenoid wing dysplasia
- Dystrophic scoliosis
  - Vertebral scalloping, rib penicillin, transverse process spindling
- Long bone dysplasia

D. Miller et al. Health supervision for children with NF 1. AAP Pediatrics. 2019

Treatment



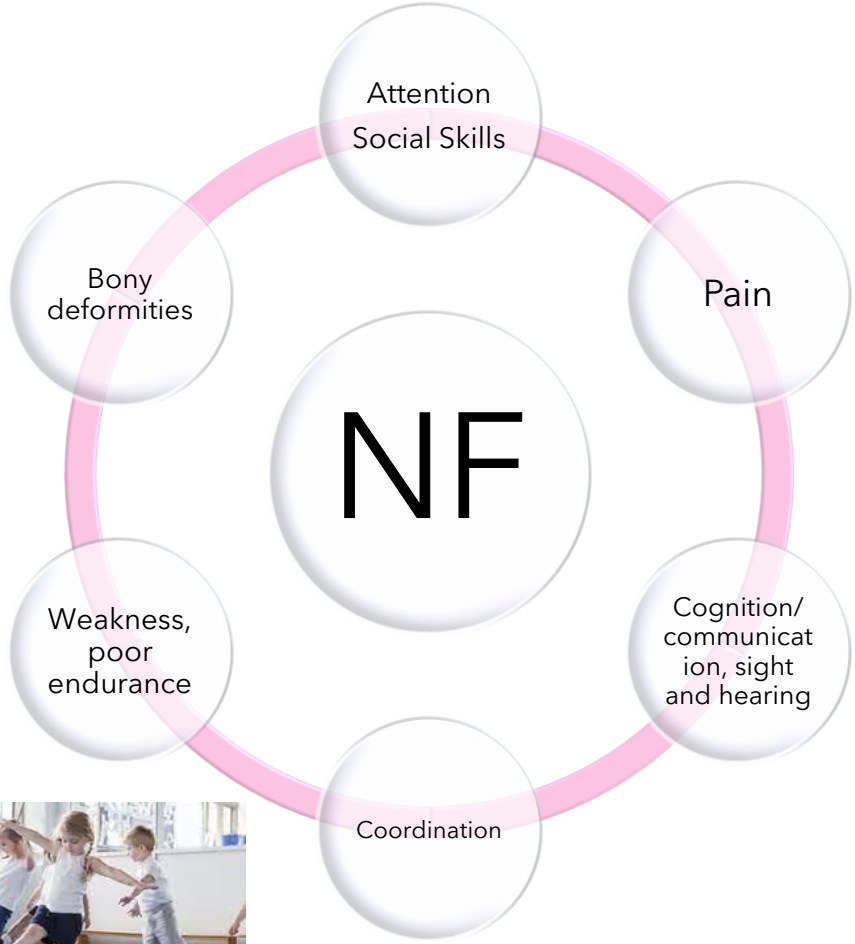
- Depends on the severity
- Observing
- Physical Therapy
- Bracing
- Surgical options

- X rays, and referral to orthopedics

Picture Credits: https://www.hudsonvalleyscoliosis.com/what-is-scoliosis/neuromuscular/
https://www.srs.org/espanol/patient_and_family/scoliosis/idiopathic/juveniles/growing_rods.htm

Let’s Exercise!

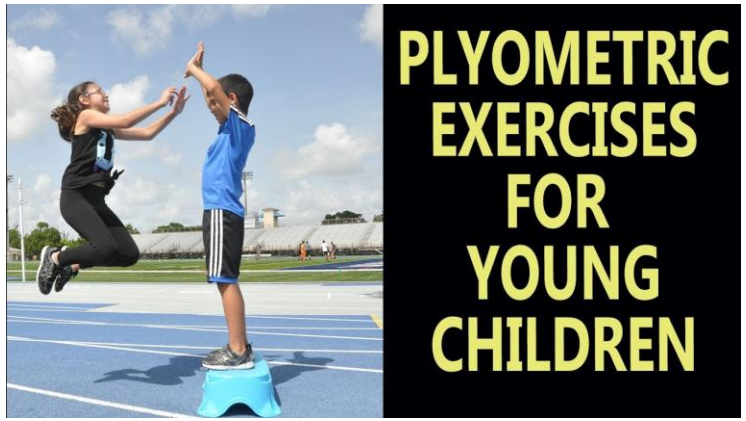
Challenges with Exercising



Picture credit: found from Google.com, may be subjected to copy right

Goals and Benefits of Exercising

- Structured program to address specific difficulties
  - Increase muscle strength
  - Prevent contractures (stretching)
  - Improve posture
  - Improve balance
  - Build stamina decrease fatigue
  - Improve functional tasks/ development
  - Decrease pain
  - Participation/ quality of life



Exercise options

Home exercise	Physical / Occupational therapies	Private / Early Intervention / School based	School based classes (i.e. gym/ P.E)
Adaptive sports	Team sports: school club, community, traveling team,	Recreational Activities: Family hiking, playgrounds	Private personal training

Bibliography

- Yang, Xiaoqin et al. “Clinical and humanistic burden among pediatric patients with neurofibromatosis type 1 and plexiform neurofibroma in the USA.” *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery* vol. 38,8 (2022): 1513-1522. doi:10.1007/s00381-022-05513-8
- Wang Y, Nicol GD, Clapp DW, and Hingtgen CM. Sensory neurons from Nf1 haploinsufficient mice exhibit increased excitability. J Neurophysiol 94: 3670–3676, 2005.
- Gross, Andrea M et al. “Selumetinib in Children with Inoperable Plexiform Neurofibromas.” The New England journal of medicine vol. 382,15 (2020): 1430-1442. doi:10.1056/NEJMoa1912735
- Nguyen, Rosa et al. “Plexiform neurofibromas in children with neurofibromatosis type 1: frequency and associated clinical deficits.” The Journal of pediatrics vol. 159,4 (2011): 652-5.e2. doi:10.1016/j.jpeds.2011.04.008
- Wolters, Pamela L et al. “Pain interference in youth with neurofibromatosis type 1 and plexiform neurofibromas and relation to disease severity, social-emotional functioning, and quality of life.” American journal of medical genetics. Part A vol. 167A,9 (2015): 2103-13. doi:10.1002/ajmg.a.37123
- Copley-Merriman, Catherine et al. “Natural History and Disease Burden of Neurofibromatosis Type 1 with Plexiform Neurofibromas: A Systematic Literature Review.” Adolescent health, medicine and therapeutics vol. 12 55-66. 19 May. 2021, doi:10.2147/AHMT.S303456
- Doorley, James D et al. “Depression explains the association between pain intensity and pain interference among adults with neurofibromatosis.” Journal of neuro-oncology vol. 154,2 (2021): 257-263. doi:10.1007/s11060-021-03826-3
- Lai, Jin-Shei et al. “Patient Reported Outcomes Measurement Information System and Quality of Life in Neurological Disorders Measurement System to Evaluate Quality of Life for Children and Adolescents with Neurofibromatosis Type 1 Associated Plexiform Neurofibroma.” The Journal of pediatrics vol. 206 (2019): 190-196. doi:10.1016/j.jpeds.2018.10.019
- Buono FD, Grau LE, Sprong ME, Morford KL, Johnson KJ, Gutmann DH. Pain symptomology, functional impact, and treatment of people with Neurofibromatosis type 1. J Pain Res. 2019 Aug 22;12:2555-2561. doi: 10.2147/JPR.S209540. PMID: 31692483; PMCID: PMC6710538.
- Xue, H., Wu, Q., Yang, Z., Wang, B., Wang, X., & Liu, P. (2021). Dissociated Deficits between Explicit and Implicit Empathetic Pain Perception in Neurofibromatosis Type 1. *Brain sciences*, *11*(12), 1591. https://doi.org/10.3390/brainsci11121591
- Buono, F. D., Larkin, K., Zempsky, W. T., Grau, L. E., & Martin, S. (2024). Understanding chronic pain in Neurofibromatosis Type 1 using the Neurofibromatosis Pain Module (NFPM). *American journal of medical genetics. Part A*, *194*(6), e63541. https://doi.org/10.1002/ajmg.a.63541

Questions?

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Thank you

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