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CHRONIC NONBACTERIAL OSTEOMYELITIS (CNO)

Developed by Iain Sander and Dr. Dax G. Rumsey for PedsCases.com.
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Introduction:

Hi everyone, my name is Iain Sander and I am a 3rd year medical student at the University of Alberta in Edmonton, Canada. This podcast was developed with Dr. Dax G. Rumsey, a Pediatric Rheumatologist at the Stollery Children's Hospital and the Division Director of the Pediatric Rheumatology Program at the University of Alberta in Edmonton. Today we will be discussing Chronic Non-bacterial Osteomyelitis, or CNO.

Objectives:

By the end of this podcast, the listener will be able to:

1) Discuss the differential diagnosis for pediatric patients presenting with non-traumatic bony pain
2) Suggest appropriate investigations for these patients
3) List the Bristol diagnostic criteria for CNO
4) Outline two options in the treatment of patients with CNO

The Case:

You are completing an elective in pediatric emergency medicine and have been asked to see Sierra, an 8-year-old girl presenting with pain below her right knee and a swollen left clavicle. She is afebrile and the rest of her vitals are normal. There is no history of mechanical trauma preceding her presentation. The patient is not visibly in pain or distress. Her parents tell you that they initially thought their daughter was having growing pains, but are now worried that she has something far more sinister like cancer, as her pain has not gone away. What is your differential diagnosis? How would you approach this patient?

Differential Diagnosis:

Because the differential diagnosis for bony pain is long (pardon the pun), it is important to prioritize the most likely and most sinister diagnoses. Some causes of non-traumatic pediatric bony pain might include:

1) Infection
    - Infectious osteomyelitis or septic arthritis
2) Malignancy:
    - Primary bone malignancy, such as Ewing Sarcoma or Osteosarcoma
    - Hematologic malignancy, including Acute Lymphocytic Leukemia (ALL)
    - Metastatic malignancy
3) Benign bone tumor:
    - Osteoblastoma
    - Osteoid Osteoma
4) Growing pains
5) CNO

History:

History of Presenting Illness:
As a starting point, there are some questions you may want to ask Sierra and her parents:

- When did you first notice the pain? For how long have you had it? These questions can help determine whether the problem is acute or more chronic.
- When is your pain worst? Does it improve or worsen with activity, or does it remain constant throughout the day? If the patient's pain is worst in the morning and improves throughout the day, an inflammatory cause such as arthritis is more likely. Also, with arthritis, there is usually joint swelling, whereas in CNO there is bony pain with no joint swelling.
- Can you do anything to help improve the pain? What makes it better? Pain of infectious or malignant etiology will likely not improve much with acetaminophen or ibuprofen.
- Have things worsened, improved, or remained constant since she first started feeling this pain? Progressively worsening symptoms would be more suggestive (but not diagnostic) of malignancy.
- Have there been changes in function: inability to go up and down stairs, get dressed, reduced play or activity, or missing school? The effect (or lack thereof) on the patient's functioning can help you get an idea of how severe the symptoms are.

After obtaining a history of the presenting illness, you will want to conduct a thorough review of systems.

- Constitutional symptoms: History of fevers, unintentional weight loss, new-onset persistent fatigue, developmental regression, or night sweats can be red flag symptoms for malignancy or infection.

- Neurologic: Associated headaches, nausea, dizziness, and changes in behavior or academic performance? These symptoms would be more concerning and indicative of systemic infection or metastatic malignancy.
- CVS/Respiratory: Dyspnea, palpitations, or syncope? These symptoms may be present in patients with septic arthritis or other more systemic illnesses.
- HEENT: Aphthous ulcers, changes in vision? These could be clues to the condition being a more systemic process.
- GI: Diarrhea or constipation? Blood or mucous in stool? Inflammatory bowel disease may be associated with CNO.
- Derm: Rashes on body, formation of ulcers or pustular lesions on palms or soles? These symptoms could be suggestive of psoriasis or pyoderma gangrenosum, conditions associated with CNO.

The remainder of the history is similar to the general pediatric history and consists of:

- Birth, Immunization, Nutrition, and Development (BIND) history
- Past medical and surgical history
- Current medications, including vitamins, natural remedies, and over the counter medications
- Allergies
- Social history, including recent travel
- Family history, with emphasis on genetic, malignant, and rheumatologic/inflammatory conditions, especially psoriasis, IBD, and ankylosing spondylitis

Back to the Case:

The patient's parents state that she has had the pain below her right knee for the past 2.5 months, with pain and swelling of her left clavicle starting about 3 weeks ago. The parents state that their daughter has experienced pain in the affected regions every day since onset and that the pain remains constant throughout the day, but seems to be most noticeable at night when she is going to bed. They often give her a dose of ibuprofen and a heating pad, which seem to help with the pain. However, overall, the pain has not improved over the past 2.5 months but has also not worsened. She is still active, going to gymnastics twice a week and has not missed school due to the pain. The patient denies having pain in other parts of her body and is otherwise healthy. There has been no joint swelling noted. Review of systems and the remainder of the history is unremarkable, apart from the patient's father having ulcerative colitis.

Physical Examination:

Like questions from the history, the physical exam will be focused around evaluating for infectious, malignant, and inflammatory causes of the bony pain. For each body system, your physical exam should consist of the following:

- HEENT

    - Palpating for lymphadenopathy, indicative of malignancy or infection
    - Conjunctival injection
    - Photosensitive rashes
    - Inspecting for oropharyngeal injection and tonsillar exudate
- Skin exam:
    - Psoriatic rash, nail pitting, or onycholysis
    - Ulcers or pustular lesions on hands and fingers
    - Petechial rashes in extremities, or over sites of pain; these dermatologic findings can be associated with rheumatologic conditions
    - Evaluating for contusions
- Respiratory Exam:
    - Crackles or rhonchi
- Cardiac Exam
    - Murmurs or palpitations; respiratory or cardiac findings may be present in disseminated infection
- Gastrointestinal exam:
    - Hepatomegaly and splenomegaly, which may be associated with malignancy
- Neurological exam:
    - Evaluating for irritability, signs of altered mentation
- MSK exam:
    - **One of the most important parts of physical exam for patients with this presentation**
    - Important to examine all joints for range of motion (ROM), pain with movement, and the presence of effusions
    - Check for tenderness to palpation of the metaphyseal regions of all long bones (e.g. around the shoulders, elbows, wrists, hips, knees, and ankles).
    - Check for tenderness to palpation along the spine, clavicles (especially medial clavicles), and mandibles, which are all common sites of involvement in CNO.
    - Muscle atrophy, loss of strength, especially around affected areas.
    - Check for sternal tenderness, often a feature of leukemia/infiltrative disease.
    - Check for the presence of enthesitis, or tenderness at the sites of attachment of tendons, ligaments, or fascia to bone.

Back to the Case:

The physical exam you perform is largely normal, apart from **an enlarged and exquisitely tender medial left clavicle and tenderness to palpation at the right tibial tuberosity**.

You are less concerned about arthritis, given the lack of morning stiffness, joint effusion(s), or limitation of joint ROM. An acute infection or hematologic malignancy are

also less likely (but not impossible), given the otherwise benign history and lack of constitutional symptoms, but you want to be cautious and avoid missing anything serious. So, you will need to decide what lab work and imaging to order.

Investigations:

For laboratory tests, an appropriate starting point might include:

- CBCd to investigate for signs of inflammation, including thrombocytosis and leucocytosis
- Acute phase reactants, including CRP, ESR, and Ferritin for inflammation in active disease
- ALT, AST, ALP, Albumin, and Bilirubin for liver function and to rule out associated autoimmune disease. It is also helpful to know baseline values of these in case the patient ends up on medications
- Urea, LDH, Creatinine, and Electrolytes, as tumour lysis can occur with rapidly progressive hematologic malignancies

In pediatric medicine, it is important to balance the risks of radiation exposure against the usefulness of the test. Let's discuss the role of different imaging modalities for investigating bony pain.

- In many cases, if the history and physical point clearly toward growing pains or similar benign cause as a diagnosis, then no imaging is necessary.
- Ultrasound is a quick bedside test that does not involve radiation exposure. It is unfortunately of little diagnostic value in the evaluation of bony pain and should therefore not be ordered.
- X-rays can be a useful starting point in the diagnostic workup of bony pain and are quicker and easier to access than CT or MRI. In CNO, x-rays can show osteolytic lesions and sclerosis in affected areas. However, it is important to consider that this modality does involve radiation exposure and is not particularly sensitive or specific.
- CT scans involve significant radiation exposure should only be used when necessary. They can be useful to look for signs of occult fracture. Also, a dual energy CT can help diagnose gout (which is extremely rare in pediatrics). CT would not be the appropriate test in this case.
- Bone Scans are a form of low-resolution nuclear medicine imaging that help to identify areas of high metabolic activity within bone. However, they involve significant doses of radiation and can be difficult to interpret in children, whose bones have active growth plates. Since bone scans do not show much detail, it is difficult to differentiate among infection, malignancy, osteomyelitis, and normal growing bones. For these reasons, they are not typically used unless MRI is not easily accessible.
- MRI is the gold standard imaging tool for the diagnosis of musculoskeletal and soft tissue lesions in pediatrics. These scans offer the best balance of high resolution images, absence of radiation, and sensitivity and specificity in identifying bone lesions. There are drawbacks to consider, however, such as

limited availability, the need to sedate young children during imaging, and high cost. In tertiary care pediatric hospitals, this is the recommended imaging modality for a case such as this. For cases of suspected or confirmed CNO, there is a whole-body MRI protocol involving coronal T1 and STIR images that takes about 30 minutes to complete.

Back to the Case:

After completing laboratory investigations and diagnostic imaging, you receive the results back. Lab investigations are unremarkable, with no evidence of inflammation, electrolyte imbalances, or abnormal cell counts. You choose to start with some x-rays (which come back normal) and order an outpatient whole-body MRI scan for this patient. Lab work and initial imaging further reassure you that there is likely no infectious or malignant process at play here. You reassure the patient and family and let them know the plan. You discharge them from the ED and instruct them to give Sierra Tylenol as needed for now.

A few weeks later, Sierra has the whole-body MRI. Your preceptor lets you know that it demonstrated widening of the left clavicle, with periosteal reaction and bone marrow edema and a lytic lesion at the right tibial tuberosity. It also showed similar inflammatory-appearing lesions at the bilateral distal tibiae and a lesion at the right proximal femur. These lesions were asymptomatic in Sierra. If radiologic findings were identified at only one site, a bone biopsy may be useful to rule out malignancy or infection.

The type of lesions identified on imaging is inconsistent with malignancy or benign bone tumours, and growing pains would have yielded normal imaging. Also, if this was infectious osteomyelitis at multiple sites throughout the body, you would expect the patient to be sicker and for the labs to be more remarkable (e.g. elevated inflammatory markers). Thus, you begin to wonder if this could be chronic nonbacterial osteomyelitis (CNO) and look into how this condition can be diagnosed and managed.

Definition:

CNO is a disease characterized by osteomyelitis, or inflammation that occurs in the bone. It is a chronic condition, persisting for 6 or more weeks. It is a non-bacterial condition, meaning that there is no microbial infection. CNO can have multiple recurrences and/or can occur in multiple bony sites simultaneously. For these reasons, a subset of CNO is termed CRMO, or chronic recurrent multifocal osteomyelitis. Many of the involved sites can be asymptomatic and just show up on imaging.

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Pathophysiology:

In contrast to autoimmune conditions, which occur due to dysfunctions of B and T cells in the adaptive immune system, CNO is an autoinflammatory condition characterized by dysfunction of the innate immune system. The exact mechanism of this condition is not fully understood, but it is thought to involve increased expression of proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, and dysregulated osteoclast behaviour [1].

Epidemiology:

CNO is a rare disorder and, while its exact prevalence and incidence remain unknown, one study estimated an incidence of up to 80 per 100,000 children [1]. CNO is primarily a disease of children and young adolescents, with peak onset between 7-12 years of age. Girls are thought to be affected 2-4 times more frequently than boys. CNO does not have a clearly identified genetic inheritance pattern but is associated with inflammatory bowel disease (IBD), psoriasis, ankylosing spondylitis, and autoinflammatory conditions, such as pyoderma gangrenosum (which is also known to be associated with IBD).

Diagnostic Criteria:

CNO/CRMO is a diagnosis of exclusion, meaning that conditions with similar presentations, such as malignancy, infection, metabolic bone disorders, and inflammatory arthritis must first be reasonably ruled out before making this diagnosis. Currently, there are no validated and widely accepted diagnostic criteria for CNO/CRMO.
However, one set of criteria were proposed by physicians at the Bristol Royal Hospital for Children in Bristol, UK. It was suggested that use of the Bristol criteria by an experienced clinician may obviate the need for a bone biopsy in some patients [2]. These criteria state that, for patients with at least 6 weeks of bony pain, the diagnosis can be made using a combination of physical exam findings, lab results, diagnostic imaging, and possibly bone biopsy [2]. A patient is said to have CNO/CRMO if he/she has:

1) The presence of bone pain (with or without localized swelling) for at least 6 weeks in the absence of significant features of infection or inflammation
AND
2) The presence of typical radiological findings showing bone marrow edema, bony expansion, lytic lesions, and periosteal reaction
AND 1 OF
i) More than one bone affected *without* significantly raised CRP (CRP < 30) OR the clavicle affected alone
OR

ii) If unifocal disease (other than clavicle) or CRP > 30, bone biopsy showing inflammatory changes (plasma cells, osteoclasts, fibrosis, or sclerosis) with no bacterial growth (while not on antibiotics).

Management and Prognosis:

The management of CNO depends on the location of lesions and responsiveness to initial therapy. In general, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), such as naproxen or celecoxib, are the first-line treatment. The exception to this rule is in the case of CNO with evidence of spinal lesions, in which case first-line treatment is a bisphosphonate, a medication that inhibits osteoclast formation and suppresses proinflammatory cytokine expression. Bisphosphonates are also used as second-line agents in patients with peripheral disease who do not respond to NSAIDs. They are not used first line in all patients due to cost and potential side effects (including flu-like symptoms, hypocalcemia, nausea, headache, and extremely rare cases of jaw osteonecrosis. Other medications that are used for refractory disease include TNF inhibitor biologics and traditional disease-modifying antirheumatic drug (DMARDs), such as methotrexate [1]. Glucocorticoids are an optional part of the treatment plan and may play a role in working to help quickly achieve remission of a flare. Steroids should be used cautiously, however, mitigating against further risk of bone fracture due to osteoporosis.

The disease course of CNO typically waxes and wanes, with eventual resolution after several years in most patients. However, it can persist into adulthood in a subset of patients. Given that this condition affects bones in childhood during their development, long term consequences of CNO without treatment can include vertebral body fractures, leg length discrepancy, muscle atrophy around the affected site(s), and (very rarely) obstruction of blood vessels and nerves, resulting in conditions like thoracic outlet syndrome [1]. To prevent significant morbidity, it is important to suspect this diagnosis in children presenting with chronic bony pain in the absence of features suggesting infection or malignancy. **Prompt referral to pediatric rheumatology for consideration of work-up, treatment, ongoing care, and monitoring is key to ensuring the best outcomes possible for these children and their families**.

Back to the Case:

After reviewing your differential diagnosis in the context of your history, physical, and initial investigations, your preceptor and you feel more confident that this patient has CNO. The ED doc decides to consult with Pediatric Rheumatology, and they agree with your clinical reasoning. She makes a referral, and they agree to see Sierra in their clinic. In the meantime, she provides a prescription for naproxen and reassures Sierra's parents that the findings were not consistent with a serious infection or malignancy, but that she likely has CNO and will be referred for further management. She sends them a handout with more information about this autoinflammatory disease.

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Over the course of this case, we:

1) Discussed the differential diagnosis for pediatric patients presenting with bony pain
2) Discussed the appropriate investigations for these patients
3) Listed the Bristol diagnostic criteria for CNO, and
4) Outlined several treatment options for patients with CNO

Summary of Key Points:

1) CNO is characterized by chronic pain and inflammation of bones lasting more than 6 weeks. This condition can occur in multiple sites and can wax and wane over multiple years.
2) CNO can be associated with other inflammatory conditions like psoriasis and inflammatory bowel disease. Your evaluation of patients with bony pain should include a thorough review of systems.
3) Life-threatening conditions, such as malignancy and infectious osteomyelitis, are important diagnoses to consider in pediatric patients presenting with bony pain. CNO should be on your differential for these patients, as well.
4) If your history and physical clearly point to growing pain or another benign diagnosis, then no imaging is necessary. In cases of more persistent or severe bony pain, plain film X-rays are a useful starting point, but MRI may be required to rule out other diagnoses.
5) In the absence of features suggestive of infection or malignancy, CNO is a condition you should consider in pediatric patients with bony pain. It is important to not mistake the presentation with growing pains as there is significant morbidity associated with unmanaged CNO. In equivocal cases, bone biopsy can be very helpful to rule out other causes.

Thank you for listening to our PedsCase on CNO/CRMO. We hope that you learned something today and that you add this condition to your differential when seeing a child presenting with bony pain.

References:

1. Ferguson, P. and Hedrich, C. (2020) Autoinflammatory Bone Diseases. In *Textbook of Pediatric Rheumatology* (8 edn), pp. 544-558, Elsevier
2. Roderick, M.R. *et al.* (2016) Chronic recurrent multifocal osteomyelitis (CRMO) - advancing the diagnosis. *Pediatr Rheumatol Online J* 14, 47. 10.1186/s12969-016-0109-1

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