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Welcome to the first issue of the McMaster Evidence Based Medicine Case Report (EBM-CR) Journal.

It is not enough for a physician to reference their education or experience alone as the basis for diagnostic reasoning or justification for a treatment decision. The concept of Evidence Based Medicine (EBM) is that clinical decisions must also be justified based on available evidence from studies. Assessing that evidence requires some fundamental knowledge of clinical epidemiology, guidelines, and, increasingly, health informatics. Yet, EBM today also goes well beyond traditional critical appraisal. Asking the right clinical questions, finding the best evidence, and evaluating that evidence is a fluid process that is integrated with a patient’s needs, values, expectations and the limitations of your own clinical skills and resources.

EBM is a lifelong practice of applying the best evidence to practical and ethical decisions for each unique patient case. Each patient and their unique circumstances challenge the notion that EBM is somehow a linear and easily replicated process. Different decisions are often made for similar patients based on the same evidence on the basis of patient goals and expectations. Clearly evidence must be individualized to each patient, yet this critical skill is rarely taught or reported.

The purpose of the EBM-CR Journal is to report and reflect on the application of evidence to real cases. By extending traditional instruction on EBM to real scenarios we hope you will learn and reflect on how to effectively practice evidence-based care.

In this issue, Yoon and Hupel describe the use of appropriate imaging to diagnose knee pain and refer for an orthopedic consultation. Griffin et al. describe an evidence-based protocol to manage deep vein thrombosis in a patient with severe hemophilia A. Geen and Connelly describe an evidence informed diagnosis of polymyalgia rheumatic based on an atypical presentation. To et al. describe new evidence for the safety of IV contrast-enhanced CT imaging. Truong et al. describe risk factors for post-concussion syndrome and mixed evidence for the effectiveness of early psychotherapy. Yeung and Shahi review the evidence for radiation as a treatment for recurrent phyllodes tumours. Kelian and Williamson describe low quality evidence to support traumatic digital amputation. Finally, Edington et al. make the case for establishing stability criteria for weaning nasal continuous positive airway pressure (NCPAP). Each of these cases exhibit the difficulty in basing individual patient decisions on high quality evidence, but also demonstrate useful approaches to meaningfully integrate available evidence.

A special thank you to all of the contributors and reviewers who made this issue possible.

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Are Knee MRIs Useful in the Diagnosis of Knee Pain in the Elderly?

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Are Knee MRIs Useful in the Diagnosis of Knee Pain in the Elderly?

Abstract

The advent of advanced imaging techniques such as MRI revolutionized the diagnosis of complex medical conditions. The increase in accessibility to MRIs has been followed by increasing inappropriate uses of this imaging modality. An example is the evaluation of knee pain in the elderly, in whom a careful history and physical exam alone can rule out common conditions such as osteoarthritis. Use of imaging in lieu of patient interview and exam leads to inappropriate use of medical resources and causes diagnostic delays. This report presents two patients presenting with knee pain that were diagnosed with arthritis: one that demonstrates appropriate diagnosis of osteoarthritis with history and clinical exam, and a second showcasing inappropriate MRI prescription leading to the same diagnosis. An MRI may be useful in the setting of an acute injury or as part of a diagnostic algorithm involving appropriate imaging prior to MRIs. A history and physical exam aided by plain knee radiographs can make the diagnosis of osteoarthritis without an MRI.

Introduction

Osteoarthritis (OA) is a degenerative disease of the joints causing significant functional loss, characterized by pain and reduced range of motion of the affected joint. Diagnostic imaging is essential in visualizing these musculoskeletal pathologies. While increasing usage of advanced imaging techniques such as magnetic resonance imaging (MRI) have expedited diagnoses and improved the quality of many lives, it is estimated that a large number of these imaging modalities are prescribed incorrectly for the evaluation of joint pain. A recent retrospective chart review of knee pain referrals in a community orthopaedic clinic found 77% of pre-consult knee MRIs were not diagnostically useful or guided management. Considering the increasing prevalence of OA with rising life expectancy, appropriate usage of imaging modalities are essential for prompt diagnosis and management as well as ensuring equitable use of healthcare resources.

The diagnosis of knee osteoarthritis is made with detailed history, a thorough physical examination and appropriate radiographic evaluations of the knee. The following two cases were chosen to illustrate appropriate and inappropriate uses of imaging techniques to confirm the diagnosis of osteoarthritis in patients presenting with knee pain.

Case Presentation

Case 1

Patient A is a 74-year-old female referred for orthopaedic consultation with a complaint of right knee pain. This has been ongoing for 15 years with an insidious onset and progression. The discomfort worsened with activity and was relieved with rest, and the patient’s ambulatory capacity had deteriorated to less than 30 minutes due to pain. The patient denied night pain and had no neurological or vascular symptoms. There were no complaints of ipsilateral groin or hip pain. The patient’s medical history was only significant for medically managed hypertension.

A physical exam of the right knee revealed a varus deformity, 10-degree flexion contracture, pseudoligamentous laxity as well as crepitus throughout range of motion. Peripheral neurovascular examination and examination of the right hip was within normal limits. Standing AP and lateral plain radiographs of the right
knee revealed end-stage osteoarthritis with severe tricompartmental joint space narrowing, subchondral sclerosis, and osteophyte formation.

Patient A was diagnosed with osteoarthritis of the right knee and underwent a total right knee arthroplasty. At the 1-year follow up, pain had improved greatly, and the patient was able to ambulate with minimal limitations.

**Case 2**

Patient B is a 75-year-old female referred for orthopaedic consultation with a complaint of left knee pain. The patient reported that this pain had been present for 2-3 years and involved the entire left leg, worsening prior to presentation. Her medical history includes breast cancer for which she received treatment with no evidence of metastatic disease.

Examination of the patient’s left knee revealed no deformity, flexion contracture, effusion, or crepitus and she demonstrated a full range of motion. Examination of the patient’s left hip revealed a decreased range of motion on all planes, most marked in internal rotation. Rotation of the left hip was painful and reproduced the patient’s symptoms. The imaging accompanying the patient’s referral only included an MRI of the left knee. The MRI findings included tricompartmental cartilage loss, subarticular bony edema in the medial compartment and a subluxated, degenerative medial meniscus with minor tears throughout its body.

After the orthopaedic evaluation, plain radiographs of the hip as well as standing and tunnel view radiographs of the left knee were obtained. These radiographs demonstrated only mild joint space narrowing of the left knee. Radiographs of the left hip revealed severe osteoarthritis changes, with severe joint space loss, osteophytes, subchondral sclerosis and subchondral cysts. The patient underwent a total left hip arthroplasty, with significant improvement in pain at 1-year follow up.

**The Evidence**

A detailed history and physical exam with appropriate radiographs of the knee can diagnose osteoarthritis, as was the case for Patient A. In contrast, the MRI of Patient B’s knee delayed appropriate diagnosis and initiation of treatment. A proper physical exam prior to orthopaedic consultation would have revealed that the patient’s left hip, and not the left knee was the painful focus. Routine hip radiographs would have confirmed the diagnosis of hip osteoarthritis. In this case, the MRI of the left knee was inappropriate and did not contribute to or change the clinical management.

A history and physical exam can quickly elicit relevant features of osteoarthritis. Insidious onset, intermittent pain that worsens with weight-bearing along with loss of function is highly suspicious for osteoarthritis in the elderly population. Joint deformity, restricted range of motion, joint effusion and crepitus are common physical exam findings in an arthritic knee. These findings are supported by radiographs showing the cardinal features of osteoarthritis: osteophyte formation, subchondral sclerosis, joint space narrowing, and subchondral cystic lesions. Arthroplasty remains the mainstay of treatment for advanced osteoarthritis recalcitrant to physical and medical therapy.

Knee MRIs are indicated in patients with knee pain in the setting of clinically significant injuries, and can also be useful in circumstances where the etiology of pain is not identifiable by history, physical exam, and radiographs. MRIs are also useful in the evaluation of benign or malignant tumours about the knee. However outside of the above indications, MRI examinations of the knee in older patients often reveal clinically non-
Are Knee MRIs Useful in the Diagnosis of Knee Pain in the Elderly?

significant degenerative lesions. The underuse of appropriate knee radiographs and overuse of inappropriate knee MRIs for the evaluation of knee pain in older patients can confound the diagnosis of osteoarthritis and cause delays in initiating appropriate care. Plain radiographs including weight bearing flexion views should be used to evaluate knee pain prior to ordering a knee MRI.

Inappropriate MRI use has implications for adverse treatment outcomes beyond delayed diagnosis and medical resource waste. Degenerative meniscal tears are common in arthritic knees and can be found in asymptomatic elderly patients’ MRIs. These findings may prompt the physician and patient alike to seek arthroscopic treatment to manage this pathology. Current literature does not support arthroscopic treatment for patients with degenerative meniscal lesions, especially in the context of knee osteoarthritis.

Learning Points

- A detailed history and physical examination along with radiographs of the knee (including standing AP/lateral views and a tunnel view) are sufficient for the diagnosis and guiding management of knee osteoarthritis.
- MRIs are useful in the diagnostic process for pain of unknown etiology with normal radiographs, as well as part of the work up for clinically significant injuries and suspected tumours about the knee.

References


Deep Vein Thrombosis Management in a Patient with Severe Hemophilia A

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Patient Consent and Privacy Declaration: Original consent provided.
Deep Vein Thrombosis Management in a Patient with Severe Hemophilia A

Abstract

Venous thromboembolism (VTE) is a common complication after orthopedic procedures that warrants routine prophylaxis during the postoperative period; however, patients with severe hemophilia A are considered to be at a lower risk due to the inherent clotting factor deficiency, and there is no general consensus in the appropriate use of deep vein thrombosis (DVT) prophylaxis among practitioners. Mr. X, a patient with a known history of hemophilia A, underwent an above knee amputation and subsequently developed a deep vein thrombosis in addition to a wound infection that failed to resolve spontaneously, posing a significant therapeutic dilemma. Currently there is a lack of evidence and guidelines on how to treat a hemophilia patient with a DVT, and in this case, he was ultimately treated with Tinzaparin and aggressive factor VIII replacement to help mitigate the risk of hemorrhage. Although the risk of DVT is considered to be lower in a factor VIII deficiency, judicious consideration of VTE prophylaxis or investigation in the presence of unilateral leg swelling is warranted in such a patient population, and the benefits of treatment must be carefully weighed against the risk of bleeding on an individual basis.

Introduction

Hemophilia A is an X-linked recessive disorder occurring in 1 in 5000 live male births, characterized by a deficiency in factor VIII. As an integral component of the clotting cascade, factor VIII acts as a cofactor, accelerating activation of factor X by factor IX. Factor VIII, produced by endothelial cells, typically circulates in the serum bound to von Willebrand factor, and is itself stimulated by the very same factor it serves to activate – factor Xa. A deficiency in factor VIII typically manifests as an increased bleeding tendency, with severity of disease being inversely proportional to the activity of factor VIII in circulation. Severe hemophilia A is associated with activity less than 1%, moderate with activity of 1 – 5%, and mild with activity 6 – 30%. Severe hemophilia is associated with earlier onset of bleeding, occasionally at birth, and an increased risk of spontaneous bleeding episode. Significant bleeding can arise with trauma or surgical procedures or can even develop spontaneously in the patient with severe hemophilia A. Intracranial hemorrhage is the most dangerous type of bleed; however, the most common type of bleed occurs in the form of hemarthrosis, arising in approximately 50% of patients. Repeated joint hemorrhage in target joints can be debilitating due to destruction of the joint, and often requires surgical treatment in the forms of debridement, fusion, synovectomy and arthroplasty.

In patients over 40 years of age, orthopedic procedures lasting longer than 30 minutes and involving the lower limb carry a high risk of venous thromboembolism (VTE). The risk of deep vein thromboses (DVT) and pulmonary embolism (PE) in this population is 10 – 20% and 1 – 5%, respectively. The judicious use of thromboprophylaxis, typically low molecular weight heparin (LMWH) or prophylactic target-specific oral anticoagulants, is common in clinical practice to reduce the occurrence of DVT and prevent potentially life-threatening complications, such as pulmonary embolism. Because hemophilia A patients, particularly severe cases, are deficient in factor VIII levels and have a propensity towards bleeding with an insufficiency in clotting, one common perioperative management option is to forgo DVT prophylaxis during orthopedic procedures to reduce the likelihood of an intra- or postoperative hemorrhage; however, the
literature is lacking to support this recommendation.  

Case Presentation

Mr. X is a 61-year-old male with severe hemophilia A and chronic pain due to hemophilic arthropathy. He underwent an above knee amputation of his right leg after four failed revision knee arthroplasties due to surgical wound dehiscence and lack of tissue healing. After the amputation there was continuous clear, non-malodorous serous drainage from the incision site, which progressed to complete dehiscence and desquamation of the surrounding skin. He was treated with a multi-antibiotic regimen, including Ciprofloxacin, Cephalexin and Metronidazole; and a wound culture, performed as an outpatient by his orthopedic surgeon, returned positive for *Pseudomonas aeruginosa*. He presented to the Emergency Department by EMS four weeks after this follow up visit when his right thigh became inflamed and unbearably painful over the period of one week. He denied fevers, chills or rigors, and review of systems was largely unremarkable. His home medications included Factor VIII 4000 U q3d, Oxyneo 320 mg TID, and Pregabalin 75 mg BID. Mr. X lived alone, ambulated by wheelchair, and performed his own wound care independently at home.

His vital signs were stable with a temperature of 36.7°C, heart rate of 79 bpm, respiratory rate of 18 rpm, blood pressure of 131/89 mmHg, oxygen saturation of 92% on room air, and he did not appear toxic or septic. His right thigh was swollen to the level of his hip and erythematous with a mottled appearance. The surgical wound was intact and lined with small fluid-filled vesicles. On palpation the skin was warmer than the contralateral limb and was tender to palpation. Sensation appeared to be intact. His CBC revealed hemoglobin of 103, with WBC of 4.9 and platelet count of 144. His INR and PTT were both within normal range at 0.9 and 22, respectively, with normal lactate levels. The creatinine level was elevated at 275. All remaining blood work was normal, and the ECG showed normal sinus rhythm. After consultation with the orthopedic surgeon, the most appropriate course of action for the wound infection management was determined to be medical therapy with antibiotics, with consideration of surgical treatment if required.

A Doppler ultrasound of the right stump was subsequently performed, revealing a possible abscess collection and an additional curious finding: a superficial femoral vein DVT. In Mr. X’s case, as a patient with a history of hemophilia A that did not receive perioperative thromboprophylaxis, it was suspected that his thromboembolism was likely provoked by the presence of infection post orthopedic surgery.

The Evidence

The discovery of a DVT in a patient with known severe hemophilia A poses a therapeutic dilemma. Hemophilia patients are generally considered to be at lower risk of thromboembolic events after orthopedic procedures, protected in theory by virtue of the coagulation factor VIII deficiency; however, this risk may increase with age. With lack of published randomized trials regarding the prophylaxis and treatment of DVT in this patient population, there is a lack of definitive guidelines to inform clinical decision making in practice and variation in clinical practice reported with some centres providing venous thromboembolism prophylaxis postoperatively and some not (Table 1).  

The recommended course of treatment in the setting of a confirmed DVT for non-hemophilia patients without contraindications is to provide immediate systemic anticoagulation, typically with unfractionated heparin, low molecular weight heparin (LMWH), fondaparinux or oral factor Xa inhibitors for the purpose of preventing a life-
threatening PE.\textsuperscript{11} Factor VIII deficiency in severe hemophilia A poses a significant risk of bleed or hemorrhage during anticoagulation, and therefore this risk must be weighed heavily against the therapeutic benefits.\textsuperscript{9} Recommended agents in this setting include those with shorter half-lives and/or reversibility, such as LMWH, unfractionated heparin and Warfarin (with a goal of an international normalized ratio between 2.0 and 3.0).\textsuperscript{14} While there are no randomized control trials outlining optimal agents or duration of treatment, some centres recommend treating initially with LMWH and subsequently bridging to oral Warfarin for a total treatment duration of 6 – 8 weeks to minimize the bleeding risk in hemophilia patients, which is shorter than the standard 12 week course followed in non-hemophilia patients with provoked VTE.\textsuperscript{14} Low molecular weight heparin is generally preferred as initial management in the general population over unfractionated heparin due to having greater predictability in anticoagulant response.\textsuperscript{14}

Resolution & Clinical Decision

Hematology and Hemophilia specialists were consulted. The Hemophilia service suggested close observation with a repeat Doppler ultrasound to assess for extension/resolution as it is not uncommon for non-progressive clots to be seen in stump veins post-amputation. The hemophilia specialist advised against inferior vena cava (IVC) filter insertion as IVC filters are typically indicated in patients with absolute contraindications for anticoagulation and come with the risk of thrombus formation at the filter site, as well as potential complications associated with removal of the filter later on.

Unfortunately, on a repeat Doppler two days later, there indeed was evidence of clot progression of greater than 2 cm, and to complicate matters Mr. X had since begun actively bleeding from his incision site and his Foley catheter. He was immediately transfused with 4000 units of factor VIII, which effectively controlled the bleeding, but the clinical question still remained: whether to place Mr. X on anticoagulation to treat the progression of the DVT, particularly in the setting of a recent bleed. Ultimately, the decision was made to begin anticoagulation with concurrent aggressive monitoring of factor VIII levels and subsequent infusions every twelve hours to maintain a factor VIII serum level of at least 30% until clot resolution.

Our hematologist selected Tinzaparin 175 IU/kg as the anticoagulant of choice due to Mr. X’s acute kidney injury and reduced creatinine clearance. Tinzaparin has been shown to demonstrate less bioaccumulation in the setting of renal impairment than other LMWH agents due to its higher molecular moiety that renders it less renal-dependent for clearance.\textsuperscript{15} Bioaccumulation of an anticoagulant agent leads to an increased risk of bleeding,\textsuperscript{15} which in the case of Mr. X is compounded by the concurrent presence of a bleeding disorder. Fortunately, Mr. X remained stable during initial anticoagulation with Tinzaparin, with no incidence of hemorrhage. He remained in hospital until evidence of clot resolution was noted on Doppler ultrasound, and was subsequently transitioned to oral Warfarin for a 6-week duration of anticoagulation treatment from the date of diagnosis of the DVT.

Learning Points

- The risk of venous thromboembolism is considered to be lower in patients with hemophilia A after orthopedic surgery; however, the risk increases with moderate and mild forms of the condition, and may increase with age.
- DVT prophylaxis postoperatively during orthopedic and other invasive
procedures must be carefully considered and the benefits individually weighed against the risk of bleeding in each patient.

- While severe hemophilia A may be a relative contraindication to anticoagulation, the use of IVC filters may not represent the most optimal choice for prevention of PE in this setting, as there is a risk of thrombus and potential bleeding complications with insertion and removal.

- VTE in patients with severe hemophilia A can be managed with factor VIII replacement and anticoagulation treatment but should occur under the direction of an experienced Hematologist, ideally in consultation with a Hemophilia Centre, and with close factor VIII level monitoring.

References


### Tables and Figures

**Table 1: Studies reporting on variation in VTE prophylaxis in hemophilia centres**

<table>
<thead>
<tr>
<th>No. of Centres</th>
<th>Location</th>
<th>Use of Thromboprophylaxis postoperatively (%)</th>
<th>Type of surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hermans et al.</td>
<td>Europe</td>
<td>26 47%</td>
<td>Invasive</td>
</tr>
<tr>
<td>Szkarija &amp; Aledort</td>
<td>USA</td>
<td>19 67%</td>
<td>Orthopedic</td>
</tr>
<tr>
<td>Pradhan et al.</td>
<td>USA</td>
<td>60 55%</td>
<td>Orthopedic</td>
</tr>
</tbody>
</table>

*Studies show no general consensus in use of VTE prophylaxis after invasive or orthopedic surgery in hemophilia patients.*
Delayed Diagnosis of Polymyalgia Rheumatica

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Patient Consent and Privacy Declaration: Original consent provided.
Delayed Diagnosis of Polymyalgia Rheumatica

Abstract

Polymyalgia Rheumatica (PMR) is the second most common systemic rheumatic disease, affecting almost exclusively those over 50 years of age. The diagnosis of PMR is based primarily on clinical presentation, with no pathognomonic test or established diagnostic criteria. This lack of specificity can result in either the over- or under-diagnosis of PMR. We describe the case of a patient with a delayed diagnosis of PMR and review steps towards evidence-based diagnosis of this disease. As well, the patient went on to develop meningococcemia most likely secondary to prednisone induced immunosuppression, which highlights yet another reason to be accurate in the diagnosis—treatment of PMR is not without risk. We hope readers will be reminded of the variable and subtle presentation of PMR and the importance of a correct diagnosis when considering patients presenting with polyarthritis.

Introduction

Polymyalgia Rheumatica (PMR) is the second most common systemic rheumatic disease after rheumatoid arthritis, affecting 6/1000 people in North America.\(^1,2\) It is a disease almost exclusively of those over 50 years old, with a higher prevalence in women than in men.\(^3\) The diagnosis of PMR is based primarily on clinical presentation, with typical symptoms of pain and morning stiffness involving the neck, shoulder girdle, and/or pelvic girdle, usually with an elevated erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP).\(^2\) However, none of these clinical or laboratory findings are specific to PMR, and although several classification criteria models have been proposed for research purposes, none have been universally accepted as a diagnostic tool.\(^2\) As well, PMR can present with a myriad of other associated symptoms, including distal musculoskeletal manifestations, carpal tunnel syndrome, or constitutional symptoms such as fatigue, depression, weight-loss, and fever.\(^1\) This variable and non-specific presentation can result in either the over- or under-diagnosis of PMR. There have been several case reports of patients meeting diagnostic criteria for PMR, who are later found to have one of a range of diseases that can masquerade as PMR, including rheumatoid arthritis, systemic lupus erythematosus, infective endocarditis, multiple myeloma, and even renal cell carcinoma.\(^4\) Conversely, if a patient presents with subtle or atypical symptoms of PMR, the diagnosis can be missed or delayed, resulting in unnecessary pain and suffering to the patient. This article outlines the best evidence for the diagnosis of polymyalgia rheumatica.

Case Presentation

An 82-year-old female with a past medical history of osteoarthritis of the lumbar spine presented to her family doctor’s office with swollen hands, diagnosed as a strained extensor tendon. Two months later she presented to the emergency department with an acute onset of increased generalized joint pain in her knees, hips and shoulders that was worse at night, and an elevated CRP of 170 mg/L (upper limit of normal 5.0 mg/L). A diagnosis of polymyalgia rheumatica (PMR) was considered by the emergency physicians, however her pain resolved with hydromorphone alone, and she remained pain-free at her follow-up family doctor’s appointment three days later. Her CRP had also fallen to 84, and it was therefore thought to be an osteoarthritic flare. Her anti-nuclear antibody (ANA) and rheumatoid factor (RF) were both normal. Her physician offered to refer her to rheumatology for an opinion on a diagnosis of PMR, however the patient was not interested at that time. One month later,
she presented to a walk-in clinic with four swollen and warm large joints, with a slightly elevated uric acid level.

She was given her first dose of prednisone 30mg for a total of three days, and remained pain free for one month. At this point, she presented once again to the emergency department with an acute onset of diffuse arthralgia of her shoulders, back, hips, knees, and this time, also feet. As well, she had chills, fever of 38.4°C, and generalized weakness. She was sore and tender in all her joints, with no obvious swelling or deformities. Her CRP was 38, and her CBC showed an elevated WBC of 16.2 x10^9/L. Urinalysis and chest radiography were normal. She was treated with empiric antibiotics and her symptoms resolved after 48 hours. She was discharged on oral Cephalexin 500mg for seven days, with no source of infection identified. A referral to rheumatology was sent by her family doctor, and she was started on prednisone for a presumed diagnosis of PMR. She remained pain free with a CRP of 26, and the diagnosis of PMR was corroborated by the rheumatologist.

Three months after her diagnosis of PMR, the patient presented to the emergency department for the third time with acute onset of low back, bilateral shoulder, and left wrist pain. She stated that this felt similar to her previous PMR flares, although she was still taking prednisone 7mg daily. Vital signs were within normal limits. All other components of her exam were unremarkable. Her bloodwork revealed WBC 18.5 x 10^9/L with a left shift likely secondary to her prednisone use. However, she also had an elevated troponin of 86 ng/L and developed atrial fibrillation requiring rate control. As well, she was in mild acute kidney failure with an elevated creatinine of 125 µmol/L, and blood urea nitrogen of 15.3 mmol/L. All other investigations were normal. She was treated with empiric IV ceftriaxone and stress steroids. Blood cultures came back positive for Neisseria meningitidis serogroup Y after 20.7 and 21.2 hours. Her CRP climbed to 172 on day six of admission. Throughout her stay in hospital she continued to feel quite well, with low back pain her only significant complaint. She was diagnosed with acute meningococcemia, and on discharge two and a half weeks later, her CRP was 12 and her acute kidney injury and atrial fibrillation had resolved.

Now seven months later, her latest CRP remains low at 10. She has not had any flares of polyarthritis and she has recently stopped prednisone treatment after approximately one year of therapy.

**Diagnostic Focus and Assessment**

**Overview of PMR**

Polymyalgia Rheumatica (PMR) is the second most common systemic rheumatic disease after rheumatoid arthritis. It is a disease almost exclusively of those over 50 years old, and is two to three times more prevalent in women than men. The exact cause of PMR is unknown, however it has been linked to an inflammatory process involving interleukin-6, and it is often associated with Giant Cell Arteritis (GCA). Risk factors therefore include age over 50, GCA, and female gender. The prognosis for PMR is excellent, as it does not increase mortality nor cause structural damage to the joints. The goal of treatment with prednisone 12.5-25mg daily is to alleviate the painful symptoms. In most patients the disease is self-limited, and prednisone can be discontinued after one to two years. However, in a subset of patients the disease course is relapsing, requiring several years of treatment.

**Diagnosis of PMR**

The diagnosis of PMR is based primarily on the history and physical exam, with key diagnostic factors including the presence of risk factors, acute onset of shoulder/hip girdle morning-
stiffness or pain greater than one hour, and rapid response to corticosteroids. Other diagnostic clues on history and physical exam are shown in Table 1.

In addition to the history and physical exam, there are a limited number of investigations that can support a diagnosis of PMR. These include an elevated ESR (91.5% of patients), and an elevated CRP (98.9% of patients). Given the non-specific nature of PMR’s clinical presentation and investigations, several classification criteria have been proposed, although none have been accepted as a diagnostic standard. The European League Against Rheumatism and American College of Rheumatology (EULAR/ACR) criteria was designed primarily as a research tool, and has a specificity of 78% and sensitivity of 68%. The EULAR/ACR criteria and our patient’s score can be found in Table 2.

Lastly, given the low sensitivity and specificity of the classification criteria, other causes of polyarthritis should be considered before a diagnosis of PMR is made (Table 3). However, routine laboratory testing should be limited, and a response to low-dose corticosteroids is supportive of the diagnosis.

**Risks of PMR Treatment**

Prednisone is a synthetic corticosteroid with diverse immunosuppressive properties. Immunosuppression is mediated through the inhibition of arachidonic acid and related inflammatory mediators and through direct suppression of cell mediated immunity. Adverse effects during short courses include hyperglycemia, induction of latent infections, and euphoric effects. Prolonged use can result in increased IgG catabolism, edema from salt and water retention, myopathy, central obesity, osteoporosis, masked infections, cataracts, increased intraocular pressure and GI ulcers. Prolonged and high dose use promotes risk for avascular necrosis of the femoral head. Prolonged courses can suppress ACTH and induce adrenal insufficiency in withdrawal. Gradual reduction is advised after prolonged course.

**The Evidence and Differential Diagnosis**

Given the case presented, it is likely that our patient did indeed have PMR, although the diagnosis was delayed by over four months. At different time points she met the EULAR/ACR classification criteria (Table 2), which has a specificity of 78% and sensitivity of 68%. As well, she did experience a prompt response to corticosteroid treatment once initiated. However, she also experienced a relapse in symptoms before prednisone was started, which confused the clinical picture and demonstrates the variable and difficult presentation of PMR. Regardless, she does not fit the diagnosis for any other conditions on the typical PMR differential, and she is now doing well after a tapering dose of prednisone, all of which support the diagnosis of PMR.

**Conclusion and Implications for Clinical Practice**

We have presented a case of delayed diagnosis of PMR in an 82-year-old female, who presented several times to both hospital and clinics before receiving a diagnosis. The important lesson for clinical practice is to remember that symptoms of PMR are nonspecific and there is no universally accepted diagnostic criteria. This makes delayed diagnosis of PMR common, and it should always be considered on a differential for polyarthritis. However, it is equally important to consider the implications of PMR treatment with prednisone. As our case elucidates, risks include immunosuppression, with our patient developing the rare complication of meningococcemia.
Learning Points

- The diagnosis of PMR is based primarily on clinical presentation, with no pathognomonic test or established diagnostic criteria.
- The consideration of alternative diagnoses to PMR should be entertained particularly if there is no response to corticosteroids.
- Polymyalgia rheumatica should always be considered when a patient presents with polyarthritis.
- The treatment of PMR with prednisone can induce immunosuppression after long-term use, with complications including life-threatening infections.

References

### Table 1: Diagnostic factors and symptoms of PMR found on history and physical exam [1,2,8]

<table>
<thead>
<tr>
<th>Diagnostic Factor/ Symptom</th>
<th>Description</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of risk factors</td>
<td>GCA, &gt;50 years-old, female</td>
<td>10-30% also have GCA</td>
</tr>
<tr>
<td>Bilateral shoulder stiffness/pain</td>
<td>Morning stiffness/pain lasting &gt;1 hour. Often cannot abduct shoulders past 90 degrees.</td>
<td>70-95%</td>
</tr>
<tr>
<td>Hip girdle stiffness/pain</td>
<td>Morning stiffness/pain lasting &gt;1 hour.</td>
<td>50-70%</td>
</tr>
<tr>
<td>Rapid response to corticosteroids</td>
<td>Complete response at 4 weeks</td>
<td>71%</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>Low-grade fever, anorexia, weight loss, malaise, depression, asthenia.</td>
<td>33%</td>
</tr>
<tr>
<td>Oligoarticular arthritis</td>
<td>Frequently wrist, metacarpophalangeal, and knee joints.</td>
<td>50%</td>
</tr>
<tr>
<td>Synovitis/bursitis</td>
<td>Can occur in peripheral joints including knee, wrist, and MCP joints. Usually mild, non-erosive, and can be asymmetric.</td>
<td>50%</td>
</tr>
<tr>
<td>Swelling/tenosynovitis/carpal tunnel syndrome</td>
<td>Swelling and pitting edema in hands, wrists, ankles, and top of feet. Tenosynovitis of long head of biceps tendon, bilateral subacromial bursitis, and trochanteric bursitis.</td>
<td>50%</td>
</tr>
</tbody>
</table>

### Table 2: EULAR/ACR Classification Criteria for PMR [8]

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Case Report Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required:</td>
<td></td>
</tr>
<tr>
<td>- &gt;50 years old</td>
<td>+</td>
</tr>
<tr>
<td>- Bilateral shoulder aching</td>
<td>+</td>
</tr>
<tr>
<td>- Abnormal CRP or ESR</td>
<td>+</td>
</tr>
<tr>
<td>Additional (must score &gt;4 points):</td>
<td></td>
</tr>
<tr>
<td>- Morning stiffness &gt;45 minutes (2 points)</td>
<td>2 points (varied)</td>
</tr>
<tr>
<td>- Pain or limited ROM at the hip (1 point)</td>
<td>-</td>
</tr>
<tr>
<td>- Absence of RF or anti-CCP (2 points)</td>
<td>2 points</td>
</tr>
<tr>
<td>- Absence of peripheral joint pain (1 point)</td>
<td>-</td>
</tr>
</tbody>
</table>
### Table 3: Differential Diagnosis for PMR [1,2]

<table>
<thead>
<tr>
<th>Disease</th>
<th>Presentation</th>
<th>Differentiating Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giant Cell Arteritis</td>
<td>New-onset unilateral headache, jaw claudication, vision loss, and tender temporal artery</td>
<td>Positive temporal artery biopsy</td>
</tr>
<tr>
<td>Late-onset Rheumatoid Arthritis</td>
<td>Presentation similar to PMR</td>
<td>No rapid response to low-dose corticosteroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elevated RF (Sensitivity 50-80%, specificity 80-90%) Positive anti-CCP (Sensitivity 61%, specificity 95%)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Muscle and joint pain, weakness in extremities, carpal tunnel syndrome, fatigue, depression, lethargy, alopecia, SOB, dry skin, weight gain, cold intolerance, vitiligo, delayed relaxation of tendon reflexes, menstrual changes</td>
<td>Elevated TSH</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>Diffuse, chronic pain</td>
<td>Normal ESR/CRP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No shoulder/hip girdle stiffness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No improvement with corticosteroids</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Muscle and joint pain, weakness in extremities, carpal tunnel syndrome, fatigue, depression, lethargy, alopecia, SOB, dry skin, weight gain, cold intolerance, vitiligo, delayed relaxation of tendon reflexes, menstrual changes</td>
<td>Elevated TSH</td>
</tr>
<tr>
<td>Paraneoplastic syndrome</td>
<td>Constitutional symptoms, proximal muscle pain</td>
<td>No response to low-dose corticosteroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tumour located on imaging</td>
</tr>
<tr>
<td>Myeloproliferative diseases (Multiple Myeloma)</td>
<td>Fatigue, bony pain</td>
<td>Abnormal serum protein electrophoresis</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>Symmetrical weakness of shoulder and pelvic girdles</td>
<td>Elevated CK</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive ANA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EMG changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diagnosis with muscle biopsy</td>
</tr>
<tr>
<td>Overuse bursitis/tendonitis</td>
<td>Unilateral shoulder involvement</td>
<td>Not bilateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal ESR</td>
</tr>
<tr>
<td>Drug Induced Infective Endocarditis</td>
<td>Statin use</td>
<td>Positive blood cultures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TTE shows vegetation on heart valve</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duke Criteria</td>
</tr>
</tbody>
</table>
Evaluating the Evidence behind Contrast-Induced Nephropathy: Use of Computed Tomography with Intravenous Contrast in a Patient with Acute or Chronic Kidney Disease

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Keywords: Computed Tomography, Contrast-Induced Nephropathy, Acute Kidney Injury

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Patient Consent and Privacy Declaration: Original consent provided.
Evaluating the Evidence behind Contrast-Induced Nephropathy: Use of Computed Tomography with Intravenous Contrast in a Patient with Acute or Chronic Kidney Disease

Abstract

The use of intravenous contrast in computed tomography (CT) has been historically linked to acute kidney injury (AKI), however recent literature has challenged the clinical relevance of this association. In this case, a 73-year-old male with a history of chronic kidney disease and recent abdominal surgery presented with abdominal pain. Due to his elevated creatinine from acute on chronic kidney injury, a CT without contrast was performed. However, the quality of imaging, the lack of clinical improvement and anticipated surgical difficulty warranted a second CT with intravenous contrast in 1 week. The improved resolution from this second study allowed definitive characterization of a diverticular abscess and allowed for more conservative intervention instead of a difficult open surgical procedure. The patient was eventually stabilized and transferred to a tertiary center for definitive management. This case illustrates one example where CT with contrast was advantageous compared to CT without contrast in clinical decision making. Furthermore, the patient did not develop clinical CIN, and the changes in his creatinine levels resolved promptly. New evidence suggests that the risks of CIN are grossly overestimated, and the use of intravenous contrast should not be delayed if it would be beneficial for clinical management.

Introduction

Intravenous (IV) contrast is commonly administered to improve the accuracy of computed tomography (CT) imaging. However, the use of contrast media has historically been linked to the development of acute kidney injury (AKI). This phenomenon is known as contrast-induced nephropathy (CIN). It is commonly defined as an increase in serum creatinine of ≥ 25% (relative) or ≥ 44 µmol/L (absolute) within 48-72 hours of contrast media exposure. Its pathophysiology is thought to consist of a combination of release of reactive oxygen species, osmotic tubular nephrosis, and ischemia of the outer medulla brought on by contrast-mediated vasoconstriction. Use of contrast media has been cited as a third leading cause of iatrogenic renal insufficiency. An incidence of as high as 25% has been reported in patients with risk factors such as pre-existing renal impairment or a combination of risk factors such as chronic kidney disease (CKD), diabetes, congestive heart failure (CHF), advanced age and concurrent administration of nephrotoxic drugs. Furthermore, in-hospital mortality rates associated with CIN have been reported to be as high as 34%. The Kidney Disease: Improving Global Outcomes 2012 guidelines recommend that patients should be screened for increased risk for CIN and if possible, alternative imaging methods should be considered in those deemed to be “high risk” for CIN. Thus, the clinician ordering CT imaging must carefully weigh the benefits of increased diagnostic accuracy using contrast media against the risk of CIN.

However, the evidence surrounding CIN and its link to CT imaging has recently begun to shift. Numerous, well done studies of the last decade have demonstrated that the risk of CIN following IV contrast has thus far been grossly overestimated. This article presents an illustrative case of a patient with abdominal...
pain where the need for greater diagnostic clarification on CT was balanced against the clinician’s aversion to predisposing the patient to CIN. We discuss in detail the evidence relevant to making such a decision.

Case Presentation

The Overview
A 73-year-old Caucasian male presented to the hospital with abdominal pain, a palpable tender mass in the left lower quadrant and discoloured urine. One month prior he had undergone exploratory laparotomy due to the presence of free air in the abdomen, however the source of the air had gone unidentified. He was eventually stabilized in hospital with a Jackson-Pratt drain and antibiotics. His medical history included COPD, gout, chronic kidney disease with several acute kidney injuries in the prior few years, and bladder cancer treated with a radical cystectomy/prostatectomy and creation of a neobladder from small bowel. He had a remote smoking history with no known drug allergies.

On examination he was generally well and did not appear septic. He had a temperature of 37.2°C, a heart rate of 112 bpm, a respiratory rate of 16 rpm, a blood pressure of 130/83 mmHg, and an oxygen saturation of 96% on room air. He had a slightly elevated leukocyte count of 11.3 x 10^9/L, a hemoglobin of 124 g/L, and a platelet count of 403 x 10^9/L. His creatinine was elevated at 215 µmol/L (eGFR 28 mL/min/1.73 m^2) with a urea of 18.5 mmol/L.

His creatinine at baseline was approximately 150 µmol/L due to his CKD. The AKI observed during admission was deemed to be prerenal in nature secondary to infection and dehydration. On the basis of his acutely elevated creatinine, the decision was made to perform a CT scan without contrast which showed an ill-defined mass in the left lower quadrant and focal inflammatory peritonitis.

Prior to Computed Tomography with Contrast
The patient was initially started on IV ceftriaxone and metronidazole for a presumed diagnosis of diverticular abscess, but he did not show signs of resolution. Given his complicated surgical history, an open surgical approach would be unlikely to obtain source control and would require excision of the sigmoid colon and neobladder. The quality of his prior CT made it difficult to identify the full nature of the left lower quadrant mass. In spite of his elevated creatinine, his poor response to treatment prompted a CT scan of his abdomen with contrast in order to fully characterize the mass and to identify a well-defined abscess that could be drained for source control as a temporary alternative to surgical intervention. It would also have identified any abnormal communications for future surgical intervention if necessary. A bolus of IV fluids was given both before and after the CT scan to protect against kidney injury. His creatinine dropped from 215 µmol/L on admission to 176 µmol/L (eGFR 35 mL/min/1.73 m^2) prior to the second CT.

Follow-Up and Outcomes
The enhanced CT scan showed a suprapubic abscess with a fistula to the patient’s neobladder, and air fluid levels bilaterally in the renal pelvis and outlining both ureters. An ultrasound-guided abscess drainage was performed. His creatinine increased from 176 to 185 µmol/L at approximately 72 hours, to a maximum of 200 µmol/L over the course of 7 days. It eventually dropped back down to his baseline. He was able to produce urine without difficulty and did not show signs of AKI after CT with contrast. The patient was eventually stabilized and transferred to a tertiary center to the surgeon who initially performed his cystectomy and created his neobladder.
The Evidence

Until the last decade, the literature strongly suggested a link between intravascular contrast media administration with acute kidney injury. However, there were two main problems with the evidence. First, many of the studies showing an increased incidence of AKI following contrast media were based on patients who underwent cardiac angiography. IV contrast administration cannot be assumed to carry the same risks as cardiac angiography because the administration in cardiac angiography is intra-arterial and suprarenal, subjecting the kidneys to a more abrupt and concentrated contrast solution. Second, most studies investigating the risk of CIN following contrast exposure did not include control groups of patients who did not receive contrast. In a recent meta-analysis, less than 1% of studies about nephrotoxicity following IV contrast exposure actually compared patients receiving IV contrast with those who did not. With lack of proper control, it is impossible to distinguish between iatrogenic (such as CIN) and concurrent physiologic (such as sepsis or cardiogenic shock) causes of AKI. For example, in discussing an apparent 100% increased risk of CIN in patients with acute pancreatitis, Wilhelm-Leen et al. argued that CT with contrast is generally reserved to rule out complications such as phlegmon or pancreatic necrosis, and therefore, only the sickest (and most likely to develop AKI as a result of their disease process) patients received contrast imaging. Furthermore, it has been shown that the serum creatinine levels of patients receiving CT can fluctuate enough to meet criteria for AKI in the presence or absence of contrast media, making it probable that the incidence of CIN has been overestimated in the literature in the absence of adequate control. More recent research addresses both problems by: 1. targeting specific methods of contrast administration; and 2. using methods such as propensity score matching and counterfactual analysis to minimize biases and confounding variables such as diagnosis, comorbidities and illness severity.

Guidelines informing the use of contrast media for CT are scarce. The guidelines set out by the Kidney Disease: Improving Global Outcomes (KDIGO) were published in 2012 and appear to be based on the aforementioned older studies: for patients who may receive intravascular contrast, clinicians should assess the risk for CIN by screening for pre-existing kidney impairment and consider alternative methods of imaging in patients who are deemed to be at increased risk for CIN. These guidelines identify an eGFR of 45 mL/min/1.73 m² as the threshold below which the risk of CIN becomes clinically important. This is in contrast to the newer guidelines published by the American College of Radiology in 2017, which recommended an eGFR of 30 mL/min/1.73 m² as the threshold. The landscape of the literature has changed dramatically since the 2012 KDIGO guidelines were published, and accordingly, these changes reflect the current updates. In 2013, Davenport et al. published two large, retrospective propensity score-matched studies on patients who either received IV contrast-enhanced or unenhanced CT imaging and only found an increased risk of CIN in patients with a pre-CT serum creatinine of >136 µmol/L or eGFR <30 mL/min/1.73 m². However, in another equally large propensity score-matched study which included the use of counterfactual analysis of patients who received CT both with and without contrast (and therefore could act as their own controls), no such relationship between CIN and IV contrast media was found at any eGFR. Diabetes, congestive heart failure, and pre-existing acute kidney injury, often touted as predisposing factors, were not found to be independent risk factors for CIN, nor was the presence of a solitary kidney. In another large propensity score-matched study on patients with stage III-IV chronic kidney disease...
disease, IV contrast was not associated with increased risk of AKI, emergent dialysis or short-term mortality.\textsuperscript{15} Most recently, in a large (n=24,267) controlled retrospective study of AKI following IV contrast media in ED patients receiving CT, there was no association between contrast exposure and AKI, chronic kidney disease, dialysis or renal transplant at 6 months.\textsuperscript{8} A recent systematic review of studies on CIN in the ICU setting and Bayesian meta-analysis has also supported this trend.\textsuperscript{16}

The major limitation to the interpretation of these observational studies is that they cannot imply nor refute causality as concretely as a randomized control trial. Additionally, a way to analyze treatment decisions such as the use of prophylactic intravenous fluids, or deciding between enhanced and unenhanced CT based on “clinical gestalt” has proven difficult to capture in the data.\textsuperscript{8,17} Eventually, randomized control trials will be required to eliminate the ambiguity that such confounding factors brings to these observational studies. The volume of evidence - especially for those with a GFR >30 mL/min/1.73 m\textsuperscript{2} - makes a compelling argument that the incidence of CIN is much lower than previously expected. Clinical decisions regarding ill patients who would likely benefit from the increased diagnostic accuracy of contrast-enhanced CT should be made with this new information in mind.

This case report is limited in that it provides only anecdotal evidence which is inherently difficult to generalize to other patient populations. Furthermore, this patient did receive pre-contrast IV hydration, an accepted method of prevention of CIN\textsuperscript{18} (the prevention of CIN is a controversial topic in and of itself and is not the focus of this case report). This could have potentially masked a CIN that would have otherwise occurred. However, the writers argue that it was not the outcome of this case that was illustrative, but rather the process. The case presented in this article is an important illustration of the need to consider the value that IV contrast can add to CT imaging versus the risk of CIN. In this case, the better diagnostic test was initially passed overdue to fears that may not be supported by the current literature. We argue that it is justified for the clinician to consider the risk of CIN when ordering IV contrast media administration, however, one should be aware that according to the best and latest evidence, this risk may be much lower than previously expected. Despite his acute chronic kidney injury as well as multiple comorbidities, the contrast-enhanced CT provided treatment-changing information without significantly altering the patient’s kidney function. That said, the lack of kidney injury in this anecdotal case could be viewed as inconsequential in considering our argument. In a similar hypothetical patient, a development of AKI following contrast exposure could well have been caused by his severe systemic illness. Rather, we contend that given the state of the literature, contrast media should not be withheld on the basis of avoiding CIN if it is felt that it is likely to provide information helpful in guiding clinical decision making. Furthermore, the patient’s eGFR just prior to his contrast-enhanced CT scan was 35 mL/min/1.73 m\textsuperscript{2}. At this level, the 2012 KDIGO guidelines suggest that the risk of CIN was clinically important and that precautions should have been taken to reduce the patient’s risk; therefore, the patient received pre-contrast IV hydration. However according to the new ACR guidelines, this patient would not have been expected to be at increased risk of developing CIN. A physician following the previous guidelines may have exposed the patient to the – admittedly low, but not nonexistent – risks of an unnecessary treatment, and demonstrates the importance of adapting to new and changing evidence. Situations such as the above confront the clinician with ambiguity regarding the best course of action. We believe that further discussion and research will be necessary in order to alleviate this ambiguity and bring clinicians onto the same page.
Evaluating the Evidence behind Contrast-Induced Nephropathy: Use of Computed Tomography with Intravenous Contrast in a Patient with Acute or Chronic Kidney Disease

Learning Points

- Below an eGFR of 30 mL/min/1.73 m², there is conflicting evidence for an increased risk of CIN with IV contrast media, and if the association exists, it is rarer than previously thought.
- Above an eGFR of 30 mL/min/1.73 m², the best evidence suggests no increased risk of CIN with IV contrast media.
- Latest studies have not found an increased risk for CIN with commonly cited risk factors such as congestive heart failure, diabetes, solitary kidney or pre-existing acute kidney injury.
- Do not delay IV contrast-enhanced imaging on the basis of avoiding CIN if it is likely to aid in clinical decision making.

References


Identification of Risk Factors and Early Intervention for Post-Concussion Syndrome in Adolescents

Identification of Risk Factors and Early Intervention for Post-Concussion Syndrome in Adolescents

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Patient Consent and Privacy Declaration: Patient details anonymized.
Identification of Risk Factors and Early Intervention for Post-Concussion Syndrome in Adolescents

Abstract

With a growing focus on concussion and related sequelae, the modern clinician must effectively identify risk factors and intervention measures to prevent disease progression. The case in point is an adolescent female which presented after an attempted suicide via antidepressant overdose. The patient had no prior psychiatric history, but had suffered a sports-related head injury that showed no immediate or subsequent neurological deficit. As such, the patient was prescribed physical and cognitive rest with no further follow-up. Retrospective review of the case identified key risk factors that placed the patient in moderate-high risk of developing post-concussion syndrome (PCS). Currently, there is no effective treatment, both pharmacologically and psychologically, for PCS. New studies have shown that early psychotherapy in high risk populations have shown prevention of PCS development.

Introduction

Concussion is a form of head and brain injury that can be caused by a direct or indirect hit to the head, face, neck or elsewhere on the body with an “impulsive” force transmitted to the head. Studies demonstrate that concussions result from a rapid rotational acceleration of the brain. Although a concussion causes changes to one’s neurological function, there is no visible structural injury and thus, no abnormality is seen on MRI or CT scans. Each year, it is estimated that more than 630,000 children and adolescents present to emergency departments (EDs) after sustaining a traumatic brain injury (TBI) in the United States. Since 2000, there has been a dramatic increase in the diagnosis of concussion amongst the children and adolescent population. Concussions usually resolve spontaneously. However, approximately one-third of children and adolescents with mild TBI will experience physical, cognitive, or emotional symptoms beyond one month after injury that can affect their quality of life. Evidence of personality changes and psychological phenomena are amongst some of the most prevalent post-concussion symptoms, yet, many clinicians fail to screen children and adolescents for these changes. This article presents a case and discusses potential screening methods and treatment of post-concussion syndrome.

Case Presentation

A 14-year-old female presented to the psychiatrist for attempted suicide via overdose of amitriptyline. The patient screened positive for major depression with active suicidal ideations and was admitted to the child psychiatry unit for closer monitoring. The patient was otherwise healthy, with no previous psychiatric history. She had sustained a concussion three months prior by a head-on-head collision in a soccer match, in which she suffered a global headache of moderate intensity, mild disorientation to place and time for 30 minutes, with no change in consciousness (GCS15), focal neurologic deficits nor signs of intracranial hemorrhage. She was assessed in the emergency department 3 hours later with return to cognitive baseline and reduced headache, and was diagnosed with mild TBI without further investigation.

Months after the injury, the patient continued to report symptoms of recurrent headaches and poor sleep, and was subsequently
prescribed Amitriptyline. She also reported increased irritability and depressed mood. The patient was also given strict orders to avoid screen-time, reading for long periods, and activities that may worsen her symptoms or cause a secondary concussion. During this time, the patient reported that she missed a lot of classes due to her concussion, a major stressor for the patient. She reported feeling more socially isolated and withdrawn.

Her concussion had played a major role in causing school and social stressors, which contributed to her suicide attempt. Based on the acuity of the situation, she was diagnosed with adjustment disorder due to mild TBI. The plan was to ensure good social supports and medication optimization. She was to attend group therapy sessions and work on her coping skills as an in-patient. This case demonstrates the importance of screening patients for any mood or psychiatric changes post-concussion.

Discussion

The diagnosis of traumatic brain injury remains largely clinical, with studies pointing towards a biochemical marker still preliminary.\textsuperscript{5,6} Use of the Standard Assessment of Concussion (SAC) criteria and Sports Concussion Assessment Tool (SCAT3) are the current practice for diagnosing head injury on the sporting sidelines.\textsuperscript{7,8} These screening tools guide the clinician in assessment of the patient’s level of consciousness, orientation, cognition, immediate memory, motor coordination, cognition, and other pertinent symptoms. Any deterioration from baseline would suggest that mild TBI may have occurred. A systematic review by the American Association of Neurology suggests the SAC has a sensitivity of 80-94\% and specificity of 76-91\% for diagnosis of mild TBI.\textsuperscript{5} However, it is recommended that these be only a guide for the clinician to point toward a possible diagnosis. Moreover, there are currently no threshold scores for either criteria for definitive diagnosis, and their most effective use requires a pre-injury assessment to establish baseline function, which may lead to issues of practicality. Immediate onset of symptoms, however, has shown positive correlation with kinetic force of impact.\textsuperscript{9}

Statistical data has shown that up to one-third of the pediatric population will return to pre-injury baseline one month following a mild TBI event, leaving the remainder to experience long-term sequelae of post-concussion syndrome (PCS).\textsuperscript{3,4} This still remains a controversial diagnosis with a broad spectrum of symptoms. The most common symptoms include headache, fatigue, psychiatric and cognitive impairment.\textsuperscript{10} It is estimated that children with history of mild TBI are 9.3 times relative risk for developing depression and mood disorders compared to the general population.\textsuperscript{11}

A recent study by Zemek et al. published in JAMA attempted to stratify risk factors in adolescents that would show predictive value for developing PCS.\textsuperscript{4} Those most at risk of developing PCS were 13-18 years old, female, and had prior diagnoses of depression, migraine and/or concussion (at 48 hours post-injury). Although our patient did not have formal diagnosis of depression, it could be suggested that her age and gender placed her in a significantly increased risk for PCS.

The hallmark of concussion treatment is to prevent further injury, and to encourage physical and cognitive rest.\textsuperscript{12} Management of PCS, especially with regards to mood disorders, is less well-defined. A systematic review by Sayegh et al. cited very modest benefit of cognitive behavioural therapy (CBT) with poor quality evidence in treatment of confirmed cases of PCS. Likewise, pharmacotherapy of depression with methylphenidate and serotonergic drugs revealed mixed results.\textsuperscript{13, 14} Preventative CBT trials in high risk patients within three months of injury showed modest decrease in development of the condition.\textsuperscript{15}
Concussion and its related long-term sequelae is a constantly evolving field with gold standards for diagnosis and treatment yet to be determined. However, evidence points towards early detection and intervention for high-risk individuals that can potentially prevent development of PCS. Given the high incidence TBI observed, this could be a highly fruitful area of study.

**Learning Points**

- Mild traumatic brain injury (TBI) is currently a clinical diagnosis, aided by SAC and SCAT3 tools.
- Up to 66% of adolescents will return to pre-injury baseline by one month, but others will have longer term pain, and psychiatric and cognitive sequelae (PCS).
- Female, age 13-18, and prior history of concussion and depression are highest positive predictors of PCS development in adolescents.
- Early CBT may prevent PCS, but psycho- and pharmacotherapy has shown mixed efficacy once formal diagnosis has been made.

**References**

Identification of Risk Factors and Early Intervention for Post-Concussion Syndrome in Adolescents


Role of Radiotherapy in Recurrent Borderline Phyllodes Tumour of the Breast with Positive Resection Margins

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Phyllodes tumour of the breast is a rare form of fibroepithelial breast tumour. These tumours can be graded according to their behaviour as benign, borderline or malignant. While surgical resection is commonly used in the management of phyllodes tumour of the breast, the role of radiation therapy in the treatment of borderline phyllodes tumour is not well elucidated. This is a case report of a 52-year-old female who presents with recurrent borderline phyllodes tumour of the breast. She has undergone surgical resection with positive margins. Since positive margins are associated with a higher risk of local recurrence, radiation therapy may have a role reducing the risk of local recurrence. Guidelines and relevant literature were reviewed to determine its applicability to the patient and if the patient should receive radiation therapy as part of her treatment plan. Currently there is no clear evidence for the use of radiation therapy for recurrent phyllodes tumours with positive resection margins. However, there is evidence of decreased local recurrence of phyllodes tumours but no effect on disease free survival for adjuvant radiation therapy after breast conservation surgery.

Case Presentation

A 52-year-old female referred to the radiation oncology department for possible adjuvant external beam radiation treatment after a wedge resection of recurrent phyllodes tumour of the left breast.

Eight years ago, the patient found a left breast lump and after excisional biopsy, this was found to be a fibroepithelial lesion measuring 4.5 cm x 4.5 cm x 2.5 cm with mild cytological atypia, plump nuclei and small nucleoli. The mitotic figures were noted to be less 1 per 10 high power fields and the lesion formed the resection margins. This was diagnosed as benign phyllodes tumour with extension to margins. The patient was then lost to follow-up.

Three years ago, the patient presented with an asymptomatic breast lump at the scar of the previous excisional biopsy and a wedge resection of the mass was performed. Pathological analysis of the mass found a 7 cm x 5.5 cm x 3.5 cm fibroepithelial lesion. This was found to have prominent stromal proliferation with mild-moderate nuclear
pleomorphism without significant nuclear atypia. Additionally, there were areas of 5 to 7 mitoses per 10 high power fields noted. Heterogeneous stromal elements were not seen. The tumour was noted to extend to resection margins. This was diagnosed as borderline phyllodes tumour with extension to margins. The patient at this point declined external beam radiation and was lost to follow-up.

This year, the patient sought medical attention for a left breast mass. Mammogram of the left breast found an 8.4 cm x 4.7 cm x 9.9 cm lesion and ultrasound of the left axilla was negative. The lesion was then surgically resected. The pathology report from the resection found a 12.1 cm x 8.2 cm x 6 cm fibroepithelial lesion with high stromal cellularity, areas of leaf-like architecture, cleft like spaces and periductal stromal condensation. The lesion was well circumscribed with no infiltrative margins. It also had variable mitotic activity of 4 to 23 per 10 high power fields, no evidence of malignant heterogeneous elements, no stromal overgrowth and no abnormal mitoses. A pathological diagnosis of recurrent borderline phyllodes tumour was made with extension to the posterior, superior, and focally anterior resection margins.

The Evidence

In the case of the patient, she was found to have recurrent borderline phyllodes tumour of the breast with positive margins. Although there are no prospective randomized data that supports radiation as a treatment to recurrent phyllodes tumours, guidelines recommended to consider radiation following the principles of soft tissue sarcomas after mass re-excision with wide margins if additional recurrence would create significant morbidity such as involving the chest wall. According to the radiation therapy guidelines for soft tissue sarcomas of the trunk, postoperative external beam radiation of 50 Gy is suggested with a boost dose of 16-18 Gy if microscopically positive margins are found postoperatively. However, the potential morbidity of the phyllodes tumour in the patient was not evaluated, making it difficult to apply the guideline.

Reviewing the relevant literature, Barth et al. and Zeng et al. investigated the treatment of malignant and borderline tumours and found that patients who received adjuvant radiation therapy following breast conservation surgery with negative margins had a decrease in local recurrence. However, adjuvant radiation therapy was not found to affect overall survival or disease-free survival. Although these studies included borderline phyllodes tumours, patients with positive margins were excluded and thus the results are not directly applied to our patient.

Kim et al. included positive margins in their study and found that in borderline phyllodes tumours, tumour recurrence was not affected by radiation therapy. However, no positive resection margin cases in their study received radiation therapy. Therefore, their conclusion could not be directly applied to the patient. Belkacémi et al. investigated prognostic factors for phyllodes tumours and found that adjuvant radiation therapy decreased local recurrence but not disease-free survival. While this study included borderline phyllodes tumors as well as tumors with positive margins, this result was reached by also including malignant tumors and negative margins in the analysis.

It is important to note that the borderline tumour groups were combined with the malignant group in the above studies and did not specifically look into the effect of adjuvant radiation therapy for borderline phyllodes tumour of the breast with positive resection margins. However, the data seems to suggest that adjuvant radiation therapy for after breast conservation surgery may decrease local
recurrence but have no effect on disease free survival. As such, adjuvant radiation therapy would be a reasonable treatment plan if the patient values decreasing the risk of local recurrence.

**Learning Points**

- Currently there is no clear evidence for the use of radiation therapy for recurrent phyllodes tumours with positive resection margins.
- There is evidence of decreased local recurrence but no effect on disease free survival for adjuvant radiation therapy of phyllodes tumours after breast conservation surgery.

**References**

Should This Digit Be Replanted?

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Abstract

Traumatic amputation of digits is ideally addressed by restoring form and function. Microvascular replantation can achieve this restoration in many but not all cases. Guidelines have been established to help surgeons in the decision-making process of whether replantation should be pursued. Given the lack of strong evidence on which these guidelines are based and the unique nature of each injury, it can be difficult to apply evidence-based medicine to an individual patient. Here we report the case of a multi-digit avulsion amputation injury which illustrates this difficulty.

Introduction

Hand injuries are common, representing 10% of accidents presenting to the ER, of which up to 9% are traumatic digital amputations. Since the first replantation of an individual digit in 1968, microsurgical techniques have advanced resulting in 75% - 92% digital replant success rates. Despite this long history, there is no single recommended reference for standard of treatment.

The existing evidence for treatment guidelines are mostly case series or anecdotal experience. As it is unethical to randomize patients to a reconstruction option, the strongest level of evidence that could be established is that of prospective case studies (level II evidence). Unfortunately, few studies exist that compare reconstruction techniques directly. Additionally, with multiple classification systems for hand injuries and different methods of communicating functional outcomes, it can be difficult to compare studies with one another.

As each case is unique, evidence-based medicine must be applied in context. Though technical considerations play a large role in determining what reconstruction options are available, patient preference remains the ultimate decider. Most individuals with an amputated digit desire that the digit be replanted, however cultural beliefs do affect how willing an individual is to accept amputation over reimplantation.

Unfortunately, research focusing on factors that help patients make holistic decisions are lacking. Existing research tends to focus on measures surgeons are interested in such as functional outcomes and adverse effects over short-term follow up. This research does not take into account whether individuals were able to return to their previous employment, or if long term mental or social well-being needs were met.

Given the lack of strong evidence-based research, personal surgical experience and knowledge shared between colleagues become the primary drivers of how to approach a case.

Case Presentation

A right hand dominant 25-year-old man was transferred from a community centre with a mangling injury of his left hand after having it caught in machinery with a rotating blade component. The patient was advised that given the nature of avulsion injuries, a decision to reimplant vs. amputate from a technical feasibility standpoint would depend on intraoperative evaluation. The patient was made aware of the lowered chance of successful reimplantation given the nature of his injury and that a longer hospital stay would result should reimplantation be chosen. Informed consent was obtained, and the patient's expressed wishes were to replant the digit if possible. On exam the index and long fingers were absent...
from the middle phalanx distally with ragged edges on remaining soft tissue. The amputated part of the long finger had been brought with the patient and kept cool. A lengthy portion of the flexor digitorum profundus (FDP) tendon remained attached to the amputated part along with portions of the muscle belly from which it had been avulsed. The rest of the hand exam was unremarkable. Total cold ischemic time of the amputated part was approximately 8 hours.

The amputated part, index and long fingers were debrided, and bony fixation completed with Kirschner wires. Prior to replantation, the amputated part of the long finger was examined under the microscope for viability. Only the radial artery appeared suitable for repair. Likewise, proximally only the radial digital artery was viable. The proximal radial artery had good pulsatile activity and consequently the decision was made to proceed with replantation. Neurovascular bundles were dissected out bilaterally, proximally and distally in preparation for replantation.

Tendons were repaired next. As the FDP tendon of the long finger had been avulsed, a large portion of it was grossly damaged and therefore resected. The FDP tendon of the index finger was no longer of any use given the level of amputation. It was therefore selected as the tendon transfer required to complete the repair of the long finger FDP. Vascular repair was then performed. Non-viable segments of the radial digital artery were resected which resulted in a distal end beyond the distal interphalangeal joint (DIP). To achieve the length required to coapt the proximal and distal ends, a vein graft was taken from the subcutaneous vein at the wrist. Orientation of the vein graft was reversed and used to repair the distal part of the digital radial artery using standard technique of adventitial stripping, luminal dilatation, heparinized saline irrigation, and multiple 10-0 nylon suture coaptation. The proximal end was then repaired in the same manner. Spasm of the artery was treated with topical papaverine application. Approximation of the digital nerves was completed, followed by repair of a dorsal digital vein and soft tissue closure. Perioperatively the replanted digit was pink, warm, and had brisk capillary refill.

Post-operatively the injured hand was kept elevated above the heart and warmed with a Bair Hugger. The patient was anticoagulated with subcutaneous heparin 5000 U twice daily and 325 mg of oral acetylsalicylic acid once daily. On post-operative day one there was an absence of capillary refill in the replanted digit. Venous congestion was observed on the second day and leech therapy was applied every four hours along with application of heparin soaked pledgets. Though venous congestion improved, the digit failed to show signs of appropriate arterial inflow. The index finger also showed ischemic changes on its distal ulnar aspect. On post-operative day five revision amputations were performed on both the long and index fingers.

The patient did have some difficulty with pain control post-operatively and was discharged home two-days post revision amputation. Though regretful that the replant did not survive, the patient was thankful that an attempt was made and was accepting of the final result.

The Evidence

Should you?
There are two reconstructive options for an amputated digit: microvascular replantation, or revision amputation. Revision amputations are faster, do not require microvascular capability, and can result in better overall hand function.\(^3\)\(^6\) Microvascular replantation is a more arduous task, requires longer hospitalization, and outcomes depend greatly on the experience of the treating surgeon.\(^7\) Asian countries with high volumes of replants and dedicated microvascular centres have achieved replant success rates of 92% compared to the North American average rate of 75%.\(^5\)
Existing guidelines for replantation focus on the injury itself taking into consideration characteristics and mechanism of the amputation, level of amputation, and number of digits affected. Thumb, pediatric, and multident injuries are considered indications to attempt replantation. Relative contraindications for replantation include single-digit amputations through zone II of the flexor tendon sheath (Fig. 1), multilevel segmental amputations, and avulsion injuries. Ischemic time for the amputated part is also taken into consideration. Given the lack of muscle tissue, digits remain viable with warm ischemic time of up to 12 hours and cool ischemic time of up to 24 hours.

In addition to injury characteristics, surgeons consider patient factors such as age, general health, and smoking status prior to pursuing a replant. Of all patient factors, smoking has the greatest negative impact on replant survival.

In this case presentation, the patient was a young healthy individual with no smoking history and a cool ischemic time of eight hours for the amputated digit. The surgeon had extensive experience in microsurgery and felt comfortable in performing a replantation procedure. Only the injury itself remained as a factor on whether to proceed.

Avulsion injuries represent a special class of injury as they have traditionally been associated with poorer survival as well as poor functional outcomes in regards to range of motion and interference with overall hand function. For avulsion injuries in North America, common practice is to perform a revision amputation. This general guideline has been challenged recently by many medical centres having greater success with replantation of avulsed fingers. In a systematic review by Sears et al., finger avulsion replant survival rates approached that of general replants with acceptable functional outcomes for range of motion and sensibility.

Informing the patient of likely functional outcomes for an intervention is an important aspect of obtaining informed consent. The level, or distance from the wrist, in which a hand injury occurs is an important predictive factor. As the index and long fingers were amputated through the middle phalanx, these injuries could correspond to either flexor sheath zone I or zone II (Fig. 2) depending on whether the flexor digitorum superficialis (FDS) remained intact. Replantation of a single digit with a zone II injury is contraindicated as the resulting stiffness of the proximal interphalangeal (PIP) joint interferes with hand function. Fortunately, the FDS tendon of the long finger remained intact and bony injuries were amenable to fixation.

**Intraoperative Considerations**

It can be difficult to promise a specific reconstructive approach until microsurgical assessment of the amputation injury is performed. Given the good functional prognosis based on the level of injury to the long finger, the patient was informed that an attempt would be made to replant the digit as long as viable vessels were found. For a replanted part to survive, arterial inflow and venous outflow must be established. Unfortunately for avulsion injuries, traction forces are placed upon vessels and nerves leading to damage distal to the site of injury. Multilevel tearing of vessel intima occurs leading to higher rates of thrombosis and there is often much greater damage than initially observed.

The steps by which replantation is performed tends to be fairly standard with bony injuries addressed first, followed by tendons, arteries, veins, and then nerves. How many vessels to repair remains somewhat controversial. As venous congestion remains a major factor in replant failure, there has been an effort to determine how many veins need to be repaired per artery. Though some studies recommend that two veins per artery should be repaired for
optimal reduction of thrombotic events, others suggest that no veins are required as long as temporary outflow measures are established. In this case, only one vein was found to be suitable for repair and this may have contributed to the venous congestion observed post-operatively.

Repair of digital arteries, when not possible in a primary end-to-end fashion, requires some type of bridging. Crossing the finger to join the radial digital artery to the ulnar is one approach but can create access problems for future repairs. In this case there was no viable ulnar digital artery on the long finger and the only option was to use a vein graft to bridge the distance. Research regarding vein donor site selection is limited to small case series and it has become common practice to harvest a vein from the volar aspect of the distal forearm as it is the closest in diameter to the digital artery.

During microvascular surgery maintaining vessel patency is crucial for successful outcomes. Irrigation is used to clear vessel lumen and topical vasodilators to treat arterial spasm are commonly applied. The use of heparinized saline for irrigation has become standard practice as it has been shown to maintain patency by reducing locally occurring thrombosis. Lidocaine and papaverine are commonly used topical vasodilators during microsurgery. Papaverine is a widely researched and popular agent. It has a quick onset of action, significantly enlarges vessel diameter, treats and to a lesser extent prevents vasospasm, and has a longer duration of action than lidocaine. Lidocaine, though less popular, has not been shown to have any less effectiveness in clinical outcomes leaving the agent of choice up to the surgeon.

Postoperative Considerations
The goal of postoperative care is to ensure establishment of stable blood flow. Thrombotic events are the largest cause of microvascular repair failure with a risk of thrombosis as high as 80% on post-operative day one, dropping to 10% by day three. Universal practices to promote stable blood flow include: keeping the replanted part elevated to prevent venous pooling, using some type of systemic anticoagulation, and keeping the area warm to prevent vasospasm.

Postoperative week one remains a critical time for antithrombotic therapy as sufficient arterial supply from neovascularization begins between day 5-7 and takes two weeks to be fully established. The choice of agent(s) for antithrombotic therapy varies between centres. Antithrombotic therapy acts on either reducing platelet function (acetylsalicylic acid), increasing blood flow/reducing blood viscosity (dextran), or counteracting effects of thrombin on platelets and fibrinogen (heparin). Aspirin alone or in combination with heparin is commonly used, and when examined by scanning electron microscope heparin treated vessels accumulate more platelets, whereas acetylsalicylic acid treated vessels accumulate more fibrin. However, a study by Khouri et al demonstrated that only postoperative subcutaneous heparin has been statistically associated with decreasing the odds of thrombosis. Since this study allowed each surgeon to use his/her own anticoagulation regimen, there has been some criticism regarding its validity.

Arterial thrombosis is the most common cause of replant failure on postoperative day one. Venous thrombosis then becomes the predominant cause. Methods of treating venous congestion include: puncturing the fingertip or removing the nail to allow for free bleeding, applying heparin pledgets, and/or applying medicinal leeches. These techniques tend to be used in combination and there are no firm guidelines as to when to use which strategy. In regards to leech therapy, hirudin, the anti-coagulant found in leech saliva, is more potent than heparin and can enter narrower vessels due to its smaller size. Interestingly a leech that attaches reluctantly and feeds slowly
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has been associated with a poorer prognosis as it indicates a lack of blood flow to the area.\textsuperscript{17}

In our patient leeches were applied every four hours. Leeches attached and fed well on postoperative day two but became more reluctant on day three. Attempts at pricking the replanted digit to encourage blood flow failed as well.

If surgical intervention can effectively salvage a failing replant it is routine to increase monitoring of colour, capillary refill, warmth, and Dopplers to every one hour for the first day.\textsuperscript{9} In our patient, the distally salvaged artery in the replanted digit had required resection to beyond the DIP where arterial diameter begun to reach the technical limits of microsurgical repair. Should additional distal resection be required, microsurgical repair would no longer be feasible. Since no salvage attempt could be made, monitoring was kept to every four hours. Though cap refill was not present on postoperative day one, slowly increasing venous congestion indicated some inflow was occurring. Unfortunately, despite leech therapy effectively addressing venous congestion, the digit did not show signs of improving arterial flow and the decision to remove the replanted part was made on postoperative day four.

**Summary**

Evidence based medicine has a history of challenging long held assumptions and establishing new approaches. Ideally all medical conditions would lend themselves well to the establishment of level I guidelines. In reality, conditions that affect a small portion of the population, have a varied population base, and have no universal outcome measures tend to result in weak evidence. Traumatic digital amputations suffer from all of these factors and are further complicated by the inherent variations in surgical treatment.

At the moment there are no standard guidelines for how long to follow digital replant patients, nor agreement over what outcomes to measure or even how to measure them.\textsuperscript{4} Practices for treatment of digital amputations and postoperative care have evolved as surgeons share their techniques and outcomes. In this case the attending surgeon was faced with the dilemma of whether to proceed with a replant and then challenged with when to accept that the replant had failed.

Given that two digits were avulsed, existing guidelines recommend that an attempt to replant should be made. Even the recommendation of revision amputation for single digit avulsion injuries has been questioned by studies demonstrating fair functional results.\textsuperscript{11} As the patient desired restoration of form and was well aware of the low chance of replant survival, the decision to attempt replantation was made.

Postoperatively the progression from successful replant to a failed one was observed. Did it make sense to try salvage interventions as long as we did? Should the patient have received an earlier revision amputation and had a shorter hospital stay as a result? These questions are difficult to answer. Despite the greater economic cost of replantation, it has been shown to be a more effective procedure than revision amputation with greater quality-adjusted life-years.\textsuperscript{18} However, a revision amputation may result in better overall hand function and can result in quicker return to function. In regard to actual economic costs, an average cost of a ward bed in Canada is $1,135 per day with 2.3 days longer mean length of stay for reimplantation when compared to amputation (5.8 and 3.5 days respectively).\textsuperscript{19,20} As per the 2016 payment schedule in BC, the cost of a digital reimplantation was $3062 compared to $251 for amputation. An approximately $5400 additional cost to reimplant a digit may be reasonable given the possibility of restoring function. However, the increased costs of
reimplantation must be weighed against the possibility of restoring function keeping in mind that many traumatic injuries occur to individuals within their prime working years. Additionally, the choice of reconstructive procedure must be made on an individualized basis taking into consideration the patient’s wishes and surgeon’s comfort level. As there is an ischemic time limit to replantation, decisions must be made in a limited amount of time as less ischemic time leads to better outcomes. Additionally, replantation or repeat operations for a failing replant must consider that over-operating in hopeless situations may subject patients to unwarranted morbidity physically and psychologically.

As the field of digital replant surgery evolves, further research into standardized communication of outcomes and postoperative care protocols will aid in establishing guidelines for better decision making by both patients and surgeons alike.

**Learning Points**

- Reconstruction options for digital amputations are determined by injury characteristics, availability of microsurgery at the treatment centre, and the microsurgical expertise of the surgeon.
- When assessing a digital amputation at community centres, it is crucial that an experienced microsurgeon be contacted for advice prior to committing to a revision amputation.
- Postoperative care should be reevaluated and adjusted based on the evolution of the replant and updated informed consent of the patient.
- Digital replantation may result in restoration of form while interfering with overall hand function. Patients must be fully informed of this possibility when choosing reconstruction options.

**References**

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Tables and Figures

Figure 1: Flexor tendon zones of the hand.

Figure 2: Lateral view of flexor tendon zones: a) flexor digitorum profundus b) flexor digitorum superficialis.
When to Wean: Towards Implementing Stability Criteria for Preterm Infants Supported on NCPAP in the NICU

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When to Wean: Towards Implementing Stability Criteria for Preterm Infants Supported on NCPAP in the NICU

Abstract

Continuous positive airway pressure (CPAP) delivered nasally (NCPAP) is commonly used in neonatal intensive care units (NICU) for preterm infants requiring respiratory support. Evidence suggests that duration and method of weaning preterm infants off NCPAP have the potential to influence health outcomes both positively and negatively. Here, we consider the case of an infant born at 29 weeks + 1-day gestation requiring respiratory support from birth who was weaned from NCPAP in our NICU. As protocolized guidelines for weaning preterm infants from CPAP are not currently available, determining readiness for weaning relies heavily on subjective assessment by senior staff. In our case, these subjective assessments correlated with stability criteria used in CPAP weaning research studies. Our case supports establishing CPAP stability and failure criteria, as they may prove useful in decision-making for less experienced practitioners. Such criteria may also enhance inter-facility communication between seasoned practitioners who have typically employed an ad hoc approach to weaning decisions.

Introduction

The fetal to neonatal transition is complex at the best of times. As the neonate enters the extra-uterine environment, initiation of effective breathing must occur rapidly with success contingent on adequate surfactant production, rapid clearance of airspace fluid, generation of adequate respiratory effort, and seamless coordination of breathing. For some infants, the added challenges associated with preterm delivery or Caesarean section necessitate resuscitative and respiratory support in the first hours and days of life. Nasal continuous positive airway pressure (NCPAP) is one such supportive strategy widely implemented in neonatal intensive care units (NICU).\(^1,2\)

Continuous positive airway pressure (CPAP) functions to reduce the work of breathing and optimize oxygenation by increasing the functional residual capacity of the newborn lungs, decreasing airway resistance, and improving thoraco-abdominal synchrony.\(^1\) Although less invasive than interventions such as endotracheal intubation, NCPAP also has important side effects suggesting that its use should be systematically titrated to optimize the care of individual NICU patients. When and how to wean neonates from NCPAP is, therefore, an important and often debated topic in neonatology. We employ an illustrative case to explore the evidence and practical management of a preterm infant transitioning from NCPAP to spontaneous breathing.

The debate around weaning preterm infants from respiratory support encompasses use of non-invasive respiratory support to wean from intubation, high flow versus low flow oxygen, intermittent positive pressure ventilation (IPPV) versus CPAP, and non-invasive high-frequency ventilation (NIHFV) as an alternative to reintubation. There are also separate considerations for special populations such as the very preterm, the very low birth weight, and those at high risk for reintubation. Despite the breadth of possible discussion points, our patient case guides the focus of this report to weaning average risk preterm infants (Table 1) from NCPAP, as this represents a common NICU scenario most medical students will be exposed to in their NICU rotations.
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Case Presentation

Infant C was born at 29 weeks + 1-day gestation weighing 1300 grams to a 33-year-old Rh-positive G3L2 woman with seroprotective antenatal screens. The prenatal course was complicated by a shortened incompetent cervix. Ms. C was put on bed rest and received Betamethasone (Celestone) at 25 weeks of gestation as 2 doses 12 hours apart. After the onset of labour, Ms. C required an emergency caesarean section due to the infant’s breech position and bulging membranes. Following a difficult extraction, Infant C was born with a significant amount of bruising; he was hypotonic with poor respiratory effort at birth. Apgar scores were 4, 9, and 9 at 1 minute, 5 minutes, and 10 minutes respectively. Positive pressure ventilation was provided for 2.5 minutes on room air, and Infant C was then transitioned to CPAP with a pressure of 6-7 cm H₂O at 40% oxygen. The infant was transferred to the NICU and received a loading dose of 13 mg/day (10 mg/kg/day) of caffeine base. He was rapidly weaned to room air (21%) but continued on NCPAP at 4-5 cm H₂O of pressure. No congenital abnormalities or malformations were noted. The tertiary care centre where Infant C received his initial care recommended he remain on NCPAP until 32 weeks of age, for a total of three weeks on NCPAP.

Therapeutic Focus and Assessment

Widely implemented protocolized guidelines for weaning preterm infants from CPAP are not currently available. The literature suggests that the approach to weaning and withdrawal of CPAP in the NICU is inconsistent among neonatologists and pediatricians, and includes: immediate removal from CPAP with or without oxygen supplementation, graded time off CPAP, reduction of airway pressure prior to discontinuation, and various combinations of these. Decisions about timing of weaning have also been noted to be largely ad hoc.

A recent Cochrane review found no evidence of either benefits or drawbacks to the use of protocol-based versus ad hoc weaning of newborn infants from mechanical ventilation in the NICU. Despite this lack of evidence, these decisions must be made routinely in the NICU and medical learners and new residents may struggle to systematically assess patients’ readiness for weaning in a setting where an ad hoc approach is the norm.

Follow-up and Outcomes

Infant C was taken off of NCPAP at corrected gestational age (CGA) of 31 weeks + 1 day and weight of 1430 grams. The patient’s oxygen requirement at this time was room air (21%), average oxygen saturation was 95-98%, and respiratory rate was approximately 30-40 breaths per minute with no chest recessions, grunting or nasal flaring noted. The patient was tolerating time off of CPAP for nursing care and did not require treatment for sepsis or any cardiovascular abnormalities. There was evidence of skin breakdown under the nose. At this time, Infant C was transitioned from 4-5 cm H₂O CPAP to low flow oxygen by nasal cannula. In the five days leading up to the discontinuation of NCPAP, the patient experienced only one apneic spell per night, all self-resolving. In the 24 hours immediately prior to the discontinuation of NCPAP, other than mild desaturations and mild bradycardia associated with oral feeding, the patient experienced no significant respiratory events.

After Infant C was transitioned to low flow oxygen by nasal cannula, he continued to have self-resolving apneic and bradycardic spells for four more days. The decision was made to optimize his caffeine dose for treatment of apnea of prematurity by increasing his caffeine base to 7.6 mg/day (5 mg/kg/day) maintenance dose. The patient was slowly
weaned off of low flow oxygen over 10 days, with oxygen saturations maintained above 88%. The caffeine base dose of 7.6 mg/day was continued and infant C allowed to self-wean with weight gain. The final self-resolving apneic episode occurred in association with gastroesophageal reflux at CGA 35 weeks + 0 days. There were no significant GI complications. Capillary pCO$_2$ was measured at 43 and 53 at 24h and 1 week after discontinuation of NCPAP, respectively. Infant C was transitioned to room air from nasal cannula at CGA 32 weeks + 5 days for a total of 11 days on low flow FiO$_2$.

Full oral feeds were achieved at CGA 36 weeks + 1 day. Screening for retinopathy of prematurity was completed at 33 weeks and 35 weeks and demonstrated a non-concerning Stage 0 in Zone 2 on both occasions. Infant C was followed with serial head ultrasounds for a grade II intraventricular hemorrhage (IVH) noted first at 30 weeks; no progression or evidence of continued bleeding was demonstrated over these four weeks and infant C was stable at discharge. Infant C required no further respiratory support for the remainder of the admission. The patient was discharged at CGA 37 weeks + 2 days.

The Evidence

Despite the wide use of NCPAP in preterm infants since the 1970s, it is in recent decades that weaning of NCPAP has emerged in discussion as an independent determinant of health outcomes in this population. While avoiding the use of invasive ventilation methods has contributed to a decrease in their associated morbidities, NCPAP is not without its’ own risks. Perceived patient discomfort, bowel distension (CPAP belly syndrome), pneumothorax, nasal trauma and deformities, obstruction due to secretions, pulmonary fibrosis, and intraventricular hemorrhage have all been associated with prolonged use of NCPAP.\textsuperscript{1,5,8}

The solution is not simply reducing amount of time on NCPAP by transitioning infants to even less invasive respiratory support methods such as nasal cannula, as some patients derive significant benefit from prolonged predictable distending pressures. Animal studies have demonstrated that longer term CPAP stimulates lung growth and reduces superoxide and inflammatory mediator production.\textsuperscript{9,10} Early weaning to respiratory support with less reliable pressure generation may be less than optimal for these patients.\textsuperscript{8} Weaning to nasal cannula prematurely is also associated with longer duration of supplementary oxygen exposure. A randomized control trial with a study population of 60 compared transitioning preterm infants (≥ 28 weeks gestation) from CPAP to either room air or to oxygen by nasal cannula. They found that there was a shorter duration of oxygen exposure (median {interquartile range}: 5 {1-8} vs 14 {7.5-19.25}) and shorter time requiring respiratory support (10.5 {4-21} vs. 18 {11.5-29}) in the group transitioned directly from CPAP to room air.\textsuperscript{8}

Evidence in the literature on how to wean infants from CPAP is growing. Notable work has been completed in Australia suggesting that sudden weaning to room air produces superior outcomes to cycling on and off CPAP in stable preterm infants < 30 weeks gestational age.\textsuperscript{11} Sudden discontinuation of CPAP was found to significantly shorten CPAP weaning time, total CPAP duration, total duration of oxygen therapy, and length of hospital admission. The incidence of bronchopulmonary dysplasia was also found to be reduced. The findings from the original randomized control trial have since been trialed in clinical practice and have remained largely consistent.\textsuperscript{12} It is increasingly becoming clear that optimizing the benefits of respiratory support requires a careful balance between ensuring adequate therapy while avoiding overexposures.
Appropriate timing of weaning has the potential to improve weaning success, reduce undue neonatal stress, and avoid re-initiation of respiratory support once discontinued. One retrospective review of 454 neonates ≤32 weeks gestational age demonstrated successful weaning at postmenstrual age of 32.9 ± 2.4 weeks, and weight at time of wean of 1611 ± 432 grams. A systematic review using these results concluded that a successful wean is, thus, more likely at corrected gestational age of 32 to 33 weeks, and weight of 1600 grams. Intubated neonates required longer time on NCPAP, as well as non-intubated infants in the setting of chorioamnionitis, anemia, and gastroesophageal reflux. Increasing birth weight was associated with younger age at successful wean in both intubated and non-intubated neonates. This particular study has identified specific numeric targets for age and weight that may predict weaning success, however, considering additional real-time measurable parameters improves accuracy and flexibility of assessments for weaning readiness.

A benefit of CPAP weaning trials conducted in recent years has been the development and refinement of stability and weaning failure criteria. Useful for standardization in research, these criteria may increasingly have clinical application. Our case highlights the potential utility of establishing a protocolized method for evaluating the readiness of individual preterm infants to commence weaning from NCPAP, particularly for new and inexperienced healthcare providers to reference. Table 2 outlines the stability criteria used in selected randomized control trials, and Table 3 describes the criteria used to determine weaning failure in those trials.

The trials emphasize similar measurements, and the target values are largely comparable across the categories. The criteria developed by Todd et al. were adjusted for the Ceasing CPAP at standard criteria (CICADA) trial based on the findings from the BOOSTII trial (2013) whose findings suggest that preterm infants with oxygen saturation targets of 85-89% had an increased mortality rate compared to those with targets of 91-95%.

We focused on the CICADA criteria for our case because they have been previously applied and studied in a clinical context. At CGA 31 weeks + 1 day and weight of 1430 grams, Infant C had not yet achieved the ideal age and weight associated with successful wean previously described. He did, however, meet the CICADA stability criteria and we were comfortable initiating his wean from NCPAP. Despite limited evidence to support one particular weaning technique over another to decrease weaning time, the criteria developed to assess weaning readiness and weaning success have been well-defined. While they may require further refinement as research continues, our case illustrates that existing criteria are useful and simple to apply in the clinical setting.

**Learning Points**

- Evidence that the duration and method of weaning preterm infants off NCPAP are themselves independent contributors to health outcomes in this population supports the need to approach these decisions systematically.
- To date, evidence to support any one specific step-by-step approach to weaning NCPAP in preterm infants is lacking.
- Establishing stability criteria may prove useful for less experienced practitioners in assessing the readiness of infants to be weaned from CPAP and for determining when to reinstate respiratory support during a weaning attempt. These criteria may also enhance communication amongst more seasoned practitioners who may
have previously used a more ad hoc approach.

References

When to Wean: Towards Implementing Stability Criteria for Preterm Infants Supported on NCPAP in the NICU


### Tables and Figures

**Table 1: Criteria for “average” risk**

1. Birth weight >1000g
2. Mean airway pressure < 8 cm on conventional mechanical ventilation; <10 cm on high-frequency ventilation
3. PaCO₂ of <65 mmHg
4. Fraction of inspired oxygen (FiO₂) <0.4
5. No severe/life-threatening congenital malformations

**Table 2: Stability Criteria used in Select Randomized Control Trials**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CICADA⁶ &amp; Todd et al¹¹ (CICADA criteria in bold)</th>
<th>Abdel-Hady et al⁸</th>
<th>Sasi et al¹⁴</th>
<th>Rastogi et al¹⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age</td>
<td>&lt; 30 weeks</td>
<td>≥ 28 weeks</td>
<td>&lt; 32 weeks</td>
<td>≤ 32 weeks</td>
</tr>
<tr>
<td>FiO₂ requirement</td>
<td>&lt; 0.30; &lt; 0.25</td>
<td>≤ 0.30</td>
<td>&lt; 0.30</td>
<td>0.21</td>
</tr>
<tr>
<td>CPAP pressure level</td>
<td>4-6 cmH₂O</td>
<td>5 cmH₂O</td>
<td>≤ 6 cmH₂O</td>
<td>5 cmH₂O</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>&lt; 60 bpm</td>
<td>&lt; 60 bpm</td>
<td>----</td>
<td>≤ 60 bpm (no tachypnea for &gt;2h)</td>
</tr>
<tr>
<td>Apneic episodes (A), bradycardias (B), &amp; desaturations (D)</td>
<td>In 1 h of previous 6 h: A: &lt; 3 self-resolving (&lt;20 s) and/or B: &lt; 3 (&lt;100 bpm) and/or D: &lt;3(≤88%; ≤86%)</td>
<td>None requiring bag &amp; mask and &lt; 6 requiring stimulation in 24h</td>
<td>-----</td>
<td>A: (&gt; 20s + B or cyanosis) ≤ 2 in 12 h &amp; ≤ 3 in 24h &amp; none requiring bag &amp; mask</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Average O₂ saturation</td>
<td>&gt; 88%; &gt; 86% or PaO₂ &gt; 45 mmHg</td>
<td>≥ 87%</td>
<td>88-93%</td>
<td>-----</td>
</tr>
<tr>
<td>Arterial Blood Gases</td>
<td>-----</td>
<td>pH &gt; 7.25 pCO₂ &lt; 60 Base deficit &lt; 8</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Tolerated time off CPAP for care</td>
<td>Yes - at least 15 minutes</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Chest recessions</td>
<td>None significant</td>
<td>None significant</td>
<td>-----</td>
<td>None significant</td>
</tr>
<tr>
<td>Time clinically stable on all parameters</td>
<td>≥ 12 hours</td>
<td>≥ 24 hours</td>
<td>-----</td>
<td>≥ 48 hours</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>≤ Grade II (exclusion criteria)</td>
<td>≤ Grade II</td>
<td>-----</td>
<td>-----</td>
</tr>
</tbody>
</table>

*Not recommended for infants with the following conditions as they were generally excluded from the trials: current treatment for patent ductus arteriosus or sepsis; severe/life-threatening congenital malformations (cyanotic heart disease, airway or chest wall abnormalities, neuromuscular or neurological disorder, chromosomal defects, pulmonary hypoplasia, periventricular leukomalacia, or hydrocephalus.*
### Table 3: Criteria for identifying failed trial off CPAP

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CICADA\textsuperscript{12} &amp; Todd et al\textsuperscript{11}</th>
<th>Abdel-Hady et al\textsuperscript{8}</th>
<th>Sasi et al\textsuperscript{14}</th>
<th>Rastogi et al\textsuperscript{15}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Decreased SpO\textsubscript{2}</strong></td>
<td>Requiring O\textsubscript{2} &gt; 29%; &gt; 25% to maintain O\textsubscript{2} sat &gt;88%; &gt;86% and/or PaO\textsubscript{2} &gt; 45 mmHg</td>
<td>&lt; 87% up to FiO\textsubscript{2} 0.60</td>
<td>Increase in FiO\textsubscript{2} &gt; 0.1</td>
<td>Requiring supplemental O\textsubscript{2} for 7 days</td>
</tr>
<tr>
<td><strong>Increased work of breathing</strong></td>
<td>Accessory muscle use Intercostal recession</td>
<td>Accessory muscle use Expiratory grunting</td>
<td>------</td>
<td>Marked retractions</td>
</tr>
<tr>
<td><strong>Respiratory rate</strong></td>
<td>&gt; 75 breaths per minute</td>
<td>&gt; 75 bpm for &gt; 1 hour</td>
<td>------</td>
<td>Persistent tachypnea</td>
</tr>
<tr>
<td><strong>Apnea (A) or Bradycardia (B) or Desaturations (D)</strong></td>
<td>Major apnea/bradycardia requiring resuscitation In 1 h of previous 6 h: &gt;2 As and/or Bs and/or Ds</td>
<td>Severe apnea requiring PPV</td>
<td>------</td>
<td>Apneic episodes</td>
</tr>
<tr>
<td><strong>Arterial Blood Gases</strong></td>
<td>pH &lt; 7.2</td>
<td>pH &lt; 7.2 pCO\textsubscript{2} &gt; 65</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td><strong>PaCO\textsubscript{2}</strong></td>
<td>&gt;65 mmHg</td>
<td>------</td>
<td>------</td>
<td>------</td>
</tr>
</tbody>
</table>
Commentary
Letter from the Dean

It is a pleasure to introduce this inaugural issue of Waterloo Regional Campus’ (WRC) Evidence Based Medicine – Case Report (EBM-CR) journal. This work is the brainchild of Dr. Andrew Costa and the collective creation of the students of the WRC.

In addition to curating a productive forum for scholarly writing, a valuable skill to carry forward into a career of questioning, inquiry, reflection and review; these reports stem from our basic curiosity with real cases and clinical applications.

As physicians our first encounters with patients, the challenges of complex cases, the natural history of disease unfolding before us progressively builds a scaffold of clinical experiences that contribute to our relational understanding of health and disease.

This journal will not only illuminate interesting cases but will provoke a review of essential concepts or unique presentations. Congratulations to all of the contributors, editors and artists in seeing your good work showcased.

In essence, this effort becomes a Waterloo Regional Campus “scholarly class yearbook” and contributes to a shared and unfailingly impressive campus legacy.

Cathy Morris
MD, MHS, FRCP
Regional Assistant Dean, Michael G. DeGroote School of Medicine,
Waterloo Regional Campus