Neurogenic heterotopic ossification: a pictorial review

ABSTRACT

Neurogenic heterotopic ossification is a condition whereby bone forms in an extra-skeletal site. It may occur in the context of major neurological insult involving the brain or spinal cord. It causes pain and restricts movement, most commonly at the hip joints. Although neurogenic heterotopic ossification is associated with significant morbidity, the diagnosis is not always considered when referring for imaging in susceptible individuals. This article highlights its key features to promote better awareness and recognition, by reviewing clinical findings and imaging of patients across various modalities including plain radiographs, ultrasound and computed tomography. The management of neurogenic heterotopic ossification is limited by late identification and consequently clinicians should always be aware of this potentially significant diagnosis. Recognition in the acute hospital setting before transfer to rehabilitation services may prevent further clinical sequelae including urinary tract infection and pressure ulcers.

This pictorial review highlights the clinical presentation and imaging features associated with neurogenic heterotopic ossification as it occurs in relation to neurological injury. Neurogenic heterotopic ossification is a condition where bone forms in a non-anatomical site, typically soft tissue. It mainly occurs in the context of traumatic, post-surgical or neurological injury (spinal cord or brain injury), but rarely it may be of genetic origin (Shore and Kaplan, 2010). In the context of neurological injury it develops in large joints below the neurological lesion, mainly at the hips. It is usually encountered in the rehabilitation setting and is often a major source of disability.

This review highlights some of the pertinent clinical and radiological findings to improve awareness of neurogenic heterotopic ossification. Radiological images of patients previously discussed at the neuroradiology multidisciplinary meeting at the National Rehabilitation Hospital, Dublin, Ireland are presented. The imaging findings across various modalities are discussed, along with recommendations and the general approach to managing these patients.

Aetiology

The incidence of neurogenic heterotopic ossification following spinal cord injury is estimated at 20–25% (Garland, 1991), and following traumatic brain injury at 10–23% (Reznik, 2015) (*Case study 1*). It can also be seen less commonly in other forms of acquired brain injury. The underlying cause of neurogenic heterotopic ossification is poorly understood, but it appears to be related to an inflammatory process (van Kuijk et al, 2002) causing mesenchymal stem cells to form osteoblasts (Buring, 1975). Previous research has explored various potential trigger mechanisms including metaplasia. Histologically heterotopic ossification can not be differentiated from the callus formation seen in normal bone healing (Garland, 1991).

Presentation

Neurogenic heterotopic ossification usually presents clinically as pain, restricted range of motion, or

CASE STUDY 1

A young woman involved in a road traffic collision suffered traumatic brain injury and spinal fractures without cord impingement (stable C2 fracture and unstable L4 fracture which underwent fixation) causing paraplegia.

At 5 months post-injury pelvic neurogenic heterotopic ossification was identified as an incidental finding on a computed tomography scan (*Figure 1*), which had been ordered for evaluation of an enterocutaneous fistula. Retrospectively looking at a computed tomography scan which had been taken 1 month post-injury (*Figure 2*) some hypodense swelling and hypoperfusion of the muscles around the right hip could be seen at the sites where the heterotopic bone later formed.

She was treated with a 12-week course of indomethacin and etidronate but with a seemingly poor response, and she progressed to develop severe bilateral pelvic heterotopic ossification, particularly on the right, shown on her next computed tomography (*Figure 3*) taken 10 months post-injury. At that time a single-photon emission computed tomography scan for further evaluation showed marked periarticular tracer uptake, especially on the right, further demonstrating heterotopic bone formation (*Figure 4*).

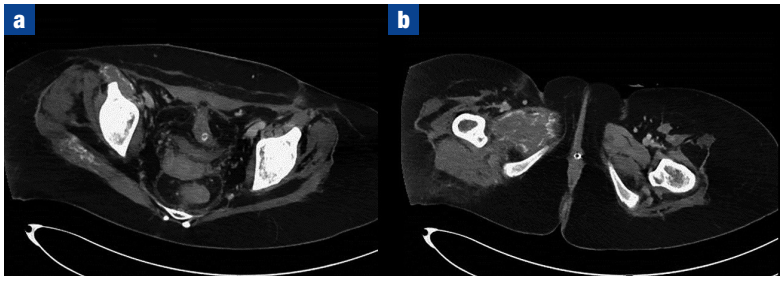

Figure 1. **a.** Superior and **(b)** inferior sections from computed tomography of the pelvis 5 months post-injury. The hypodense swelling went on to progressively ossify, giving the classical appearances of heterotopic ossification in the same muscle groups.

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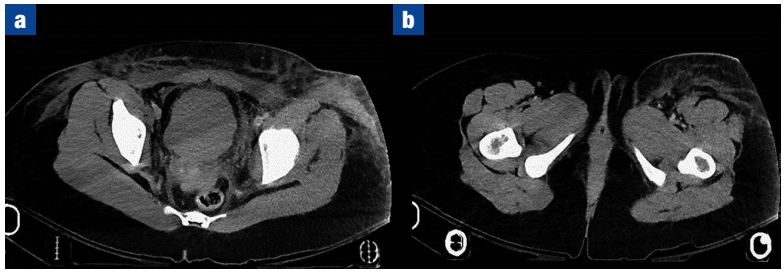

Figure 2. **a.** Superior and **(b)** inferior sections from initial computed tomography of the pelvis 1 month post-injury showed hypodense swelling and hypoperfusion (post contrast) of the periarticular muscle groups of the right hip, although this was not recognized as heterotopic ossification at that stage.

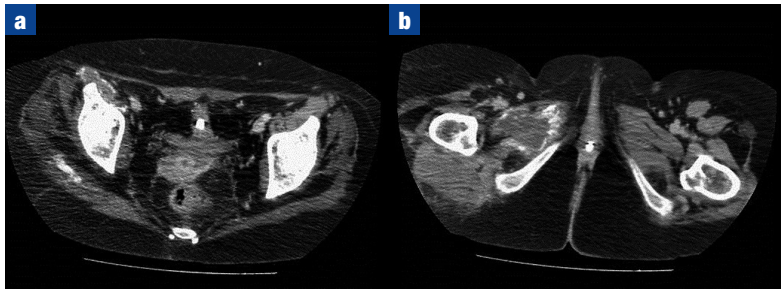

Figure 3. **a.** Superior and **(b)** inferior sections from final computed tomography of the pelvis 10 months post-injury shows extensive heterotopic ossification around the right hip in all muscle groups.

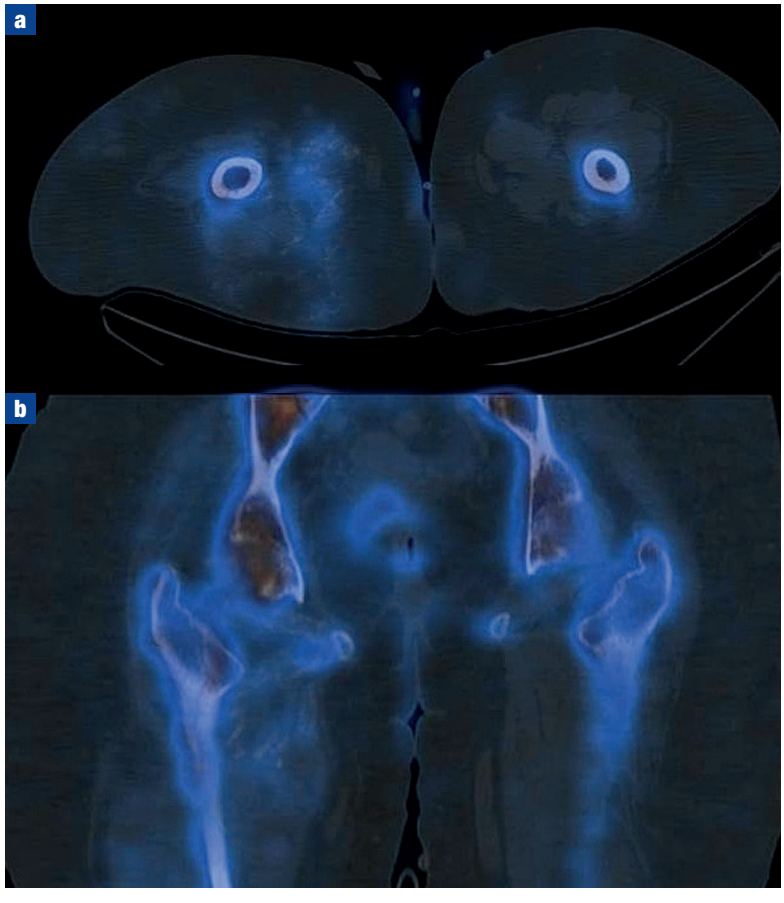

Figure 4. **a.** Axial and **(b)** coronal sections from single-photon emission computed tomography performed 10 months post-injury also demonstrate marked periarticular tracer uptake at the right hip indicating heterotopic bone formation.

occasionally as limb swelling. It is often first seen on plain radiograph although, as described by Falsetti et al (2011) and others, it can be detected earlier on ultrasound and often more fully appreciated on computed tomography and bone scintigraphy. Single-photon emission computed tomography will readily show increased radiotracer uptake at sites of heterotopic bone formation (*Figure 4*) and has the highest sensitivity of all in detection of early heterotopic ossification (Ghanem et al, 2019) but does not form part of the usual work-up pathway because of limitations of cost and availability.

In a typical district hospital setting ultrasound is generally accepted as the best choice for detection of early neurogenic heterotopic ossification. It also has the added advantage of being able to assess for deep vein thrombosis, which may be the mode of initial presentation and with which there may be some diagnostic overlap (van Kuijk et al, 2002). Neurogenic heterotopic ossification itself is associated with raised levels of D-dimers (Perkash et al, 1993), so Doppler ultrasound may identify neurogenic heterotopic ossification as an alternative diagnosis in patients originally referred with a queried deep vein thrombosis (*Case study 2*) (Bang et al, 2015). As well as adding secondary disability to those with a primary neurological insult, those who develop neurogenic heterotopic ossification are at increased risk of complications such as urinary tract infection, secondary osteoporosis and pressure ulcers (Wittenberg et al, 1992).

Management

Management of neurogenic heterotopic ossification can be problematic and highly dependent on the stage at which it is identified. In the neurological rehabilitation setting patients will invariably be receiving physiotherapy related to their primary diagnosis. The use of physiotherapy to improve passive range of motion as a specific treatment for neurogenic heterotopic ossification had previously caused concern owing to fears around micro-fractures with the heterotopic bone causing further soft tissue injury or even haematoma (Rossier et al, 1973). The consensus now is that it bestows overall benefit in terms of maintained joint range (Aubut et al, 2011).

Pharmacological management in the first instance comprises indomethacin which was shown by Banovac et al (2001) to decrease overall incidence and delay onset of neurogenic heterotopic ossification in patients with spinal cord injury if given prophylactically. Similarly etidronate (a bisphosphonate), which inhibits osteoclastic activity initially leading to a relatively greater decrease in bone resorption, decreases the incidence of neurogenic heterotopic ossification in both acquired brain injury and spinal cord injury cohorts when given for 6 months prophylactically from the onset of injury. The response to treatment once disease is established is very mixed and some patients may ultimately need surgery or radiation. Studies using etidronate to treat neurogenic heterotopic ossification once it had been diagnosed by radiographs in

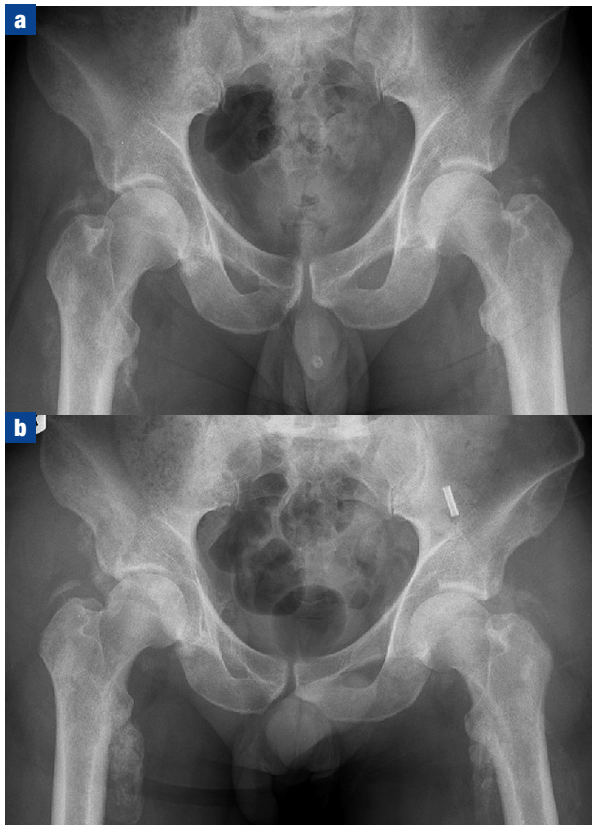

Figure 5. **a.** At 3 months post-injury there are areas of moderately extensive neurogenic heterotopic ossification around both hips. **b.** At 8 months post-injury the areas of neurogenic heterotopic ossification have increased in size and are more defined. There is new increased density seen superior to the right hip and anterior to the right acetabulum and an increase in size of the neurogenic heterotopic ossification superior and lateral to the left hip joint space. There is well-demarcated extensive mature heterotopic bone extending distally from the level of the lesser trochanters along the femoral shafts.

patients with spinal cord injury found it was ineffective in halting disease progression but commencing treatment before there was positive radiographic evidence was shown to lower incidence. A systematic review by Aubut et al (2011) concluded that both etidronate and indomethacin are effective as prophylactic therapies in patients with spinal cord injury and may have also a role in patients with traumatic brain injury.

Once neurogenic heterotopic ossification has formed, surgery is the most effective treatment, albeit with a high risk of recurrence. Surgeons will typically wait for neurogenic heterotopic ossification to mature before resection to decrease the risk of recurrence, but this can take years and leave the patient with significant discomfort and disability during this time. Aubut et al (2011) recommend considering a combined pharmacological and surgical approach in these patients, in addition to range of motion exercises. Radiotherapy is effective at halting progression and can be used as an adjunct to surgery, but is not practical as a prophylactic treatment given the number of sites that would need to be treated and the associated side effects.

CASE STUDY 2

A middle-aged man with a background of T1 American Spinal Injury Association (ASIA) B spinal cord injury was referred initially on two separate occasions for lower limb ultrasound with a query deep vein thrombosis (2 months post-injury), a common differential diagnosis and method of presentation. He had bilateral thigh swelling, which was worse on the right. On the first imaging referral the neurogenic heterotopic ossification went unrecognized as a dedicated vascular ultrasound study was negative for deep vein thrombosis. He was re-referred because he had worsening hip pain. Plain radiograph later that month showed neurogenic heterotopic ossification (*Figures 5* and *6*).

He was treated with 12 weeks of etidronate after which there seemed to be some clinical improvement in terms of range of motion at the hips and degree of swelling. However, 2 months after finishing treatment the swelling returned and pelvic X-ray showed progression of disease, confirmed by ultrasound of the thigh a month after that (*Figure 5a*). He was treated with another 12-week course of etidronate after which a surveillance pelvic X-ray showed no change around the femoral neck but unfortunately new neurogenic heterotopic ossification around the distal femur. No further treatments have been considered to date.

This case highlights the need to consider performing or referring for musculoskeletal ultrasound at the same time as referring for vascular ultrasound (Duplex) scan of lower limbs to rule out deep vein thrombosis. Neurogenic heterotopic ossification alone can present with unilateral lower limb swelling and cause raised D-dimer levels, so in a patient with significant neurological injury it should be considered a major differential in what is generally seen as a deep vein thrombosis-type picture.

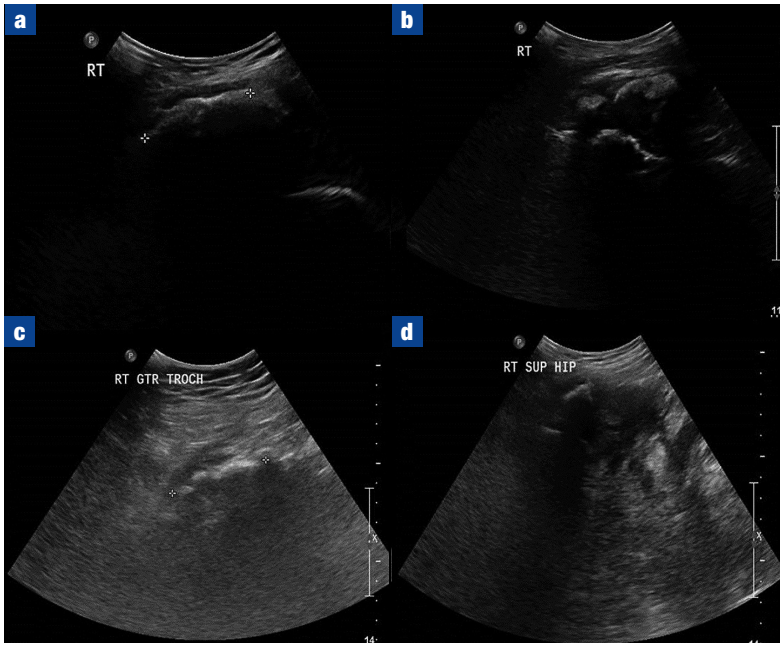

Figure 6. **a–d.** Targeted ultrasound at 8 months post-injury confirmed the presence of moderately large areas of calcified and non-calcified soft tissue abnormality anteriorly around both hips and extending superiorly on the right side. These are mainly composed of echogenic sheets of tissue consistent with calcification and ossification, although less well-defined hypoechoic foci are also seen anterior to the right hip joint with internal vascularity suggestive of less mature disease.

KEY POINTS

- Neurogenic heterotopic ossification is a process whereby ectopic bone forms around joints in characteristic patterns in patients diagnosed with spinal cord injury or traumatic brain injury. It causes pain and restricts movement, most commonly at the hip joints.
- Increased awareness of neurogenic heterotopic ossification in the acute setting before transfer to rehabilitation services may facilitate earlier diagnosis of this condition, which has potentially serious consequences including urinary tract infection, pressure ulcers and pneumonia.
- Once neurogenic heterotopic ossification has developed it responds poorly to medical therapies. Early diagnosis allows early management and reduces progression and complications.
- Neurogenic heterotopic ossification should be always be considered in the differential for patients with spinal cord injury and leg swelling who are referred for Doppler ultrasound. Neurogenic heterotopic ossification should be looked for in the soft tissue around the hips. D-dimer levels may be also be raised in patients with neurogenic heterotopic ossification which can blur the distinction before imaging.
- Characteristic features of neurogenic heterotopic ossification are seen on ultrasound and plain radiography, but are often present earlier on ultrasound. Other imaging modalities (e.g. computed tomography and bone scintigraphy) may help.
- Given its high prevalence among patients with traumatic brain injury and spinal cord injury one should always be aware of this potentially relevant finding when reviewing imaging on susceptible patients, as there are rehabilitation challenges and management issues to be considered.

Awareness of neurogenic heterotopic ossification

Given the above it follows that early detection is the best facilitator of successful treatment. However, awareness of neurogenic heterotopic ossification can be limited, particularly in acute hospital settings.

Conclusions

Once neurogenic heterotopic ossification has developed it responds poorly to medical treatments, with the only compelling evidence for their use so far being in the prophylactic context. More studies are required to establish whether there is any benefit when medical therapies are commenced with the onset of early radiographic disease. Future studies could also assess who the highest risk patients are, and whether screening these with for example ultrasound of both hips, would help reduce morbidity. **BJHM**

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