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Ultrasonographic diagnosis of neurogenic heterotopic ossification in patients with severe acquired brain injury admitted to a neurorehabilitation unit.

Short title: Ultrasound of heterotopic ossification

Abstract

Purpose: to illustrate the ultrasonographic (US) and Power Doppler US (PDUS) features of neurogenic heterotopic ossification (NHO) in consecutive patients with severe acquired brain injury, to evaluate the role of bedside US in diagnosis of NHO, to study incidence of clinical NHO in this neurorehabilitation setting.

Methods: Ninety-two (92) consecutive patients with severe acquired brain injury underwent clinical and laboratory screening to pose suspect of NHO. In 6/92 patients bedside US confirmed the clinical suspect of NHO. US diagnosis of NHO was then confirmed by other imaging methods.

Results: the incidence of clinical NHO was 7% (one patient with multifocal involvement). In NHO of hip US demonstrated the classical pattern of zone phenomenon, and PDUS demonstrated vascular signal within mineralized NHO and in outer hypoechoic area. No vascular signal was observed in the central hypoechoic core. In NHO of knee and elbow only a heterogeneously hypoechoic mass or hyperechoic mineralized mass were respectively evident, with vascular signals within the lesions. Spectral wave analysis (SWA) demonstrates low resistance vessels in NHO.

Conclusions: bedside US is a useful and cheap tool in diagnosis of NHO. PDUS adds data about neoangiogenetic activity of NHO.
Introduction

Heterotopic ossification is the development of mature lamellar bone (by endochondral ossification) in periarticular soft tissues. This process is frequently associated with neurological disorders (spinal cord injury, hemiplegia due to stroke or traumatic brain injury, encephalitis) and it is defined neurogenic heterotopic ossification (NHO)\(^1\)\(^-\)\(^3\). However, heterotopic ossification has been described with the same features in burns, trauma and joint arthroplasty\(^4\)\(^,\)\(^5\). Other terms are used to describe this phenomenon, such as paraosteoarthropathies, myositis ossificans, heterotopic bone formation.

NHO can lead to severe limitation of the range of motion (ROM) and even complete ankylosis of peripheral joints\(^1\)\(^,\)\(^4\). As not-surgical treatment of NHO, even if controversial, should prevent endochondral ossification, diagnosis should be made before calcification of involved soft tissue\(^1\)\(^,\)\(^3\)\(^,\)\(^6\)\(^,\)\(^7\).

Though NHO could begin within few weeks after neurological injury, diagnosis is often delayed. Early clinical signs include decreased ROM, local pain and firm swelling, erythema and warmth. The clinical features of the early inflammatory phase mimic tumour, infection, deep venous thrombosis (DVT) and acute arthritis\(^1\)\(^-\)\(^4\)\(^,\)\(^8\). Laboratory findings may not be helpful in early diagnosis. In particular, a rise of serum alkaline phosphatase (AP), hydroxyprolinuria and erytrocite sedimentation rate (ESR) is reported but it is very aspecific\(^1\)\(^,\)\(^3\).

Diagnostic radiographic or computed tomography (CT) findings may not appear for one month. Three-phase 99m Technetium bone scanning is a sensitive diagnostic tool for NHO, but its low specificity leads to difficulty in discriminating NHO from other inflammatory, traumatic or degenerative process of the skeleton. Also magnetic resonance imaging (MRI) has proved limited role in the early diagnosis of NHO because of its moderate specificity, high cost and necessity of contrast\(^1\)\(^,\)\(^9\)\(^-\)\(^11\).
Gray-scale ultrasonography (US) is proved to be a sensitive imaging method in soft tissues lesions, calcifications and bone-related diseases \(^{12,13}\). Moreover US has high specificity in early diagnosis and follow-up of NHO, allows differentiation from muscle tears, haematoma, infection, DVT and soft tissues tumour \(^{1,2,8,14-20}\). US has the advantage of bedside application, it is easy to perform, repeatable and inexpensive and requires no radiation. Doppler US has proved to be a reliable tool for semiquantitative assessment of the vascularity of the soft tissue \(^{12}\). As demonstrated in a recent work Doppler US can detect hypervascularization inside and outside HO \(^2\).

The aim of this study was to evaluate the role of bedside US in early diagnosis of NHO, to define the incidence of clinical NHO in this setting and to describe US and power Doppler US (PDUS) features of NHO.

**Materials and Methods**

Ninety-two consecutive inpatients transferred from Neurosurgery or other intensive care unit and referred to our neurological rehabilitation unit from September 2007 to October 2008 with severe acquired brain injury and clinical suspect of NHO underwent bedside US and PDUS examination. Clinical suspect of NHO derived from reduction of ROM of a joint, with or without local swelling, rising of AP and/or ESR and C-reactive protein (CRP).

Location, etiology and severity of the neurological lesion and risk factors for NHO (like DVT, spasticity, pressure sores, and infection) was recorded.

In all US positive cases for NHO, diagnosis was confirmed with radiography or CT, and three-phase scintigraphy.

In all NHO patients a therapy was initiated with: indometacin 50 mg bid for 15 days, disodium etidronate 300 mg bid per 6 months, 6-methylprednisolone 8 mg until normalization of ESR, and cautious joint mobilization.
Bedside US examination were carried out using a SonoSite (Bothell, USA) Titan with a 5-10 MHz linear transducer (frequency variations depending on site and depth of the lesion). Each US examination was carried out with both longitudinal and transverse scans by the same operator, with the same machine setting. The technical parameters of power Doppler US were: lowest pulse repetition frequency (PFR) avoiding flash artifact, highest gain level without background noise and low filter. The intensity of vascularity at PDUS analysis of the NHO lesions was rated on a semi-quantitative 4-point scale as follows: grade 0= no flow signal; grade 1= 1-2 flow signals (only as coloured spot); grade 2= 2-5 flow signals (both coloured spot and/or definite vessels without secondary branching); grade 3= >5 flow signals or vascular tree or diffuse blush with vessel boundaries not distinguishable. A spectral Doppler tracing was obtained to confirm that each color signal represented true arterial flow and spectral wave analysis (SWA) was performed in order to define two indices: Pulsatility Index (PI) and Resistance index (RI). In particular the latter, defined as (maximum systolic velocity- end diastolic velocity)/ maximum velocity, was recorded as it correlates with increasing peripheral resistance.

Results

Six patients over 92 (7 %) with severe acquired brain injury had clinical and US evidence of NHO. The demographic and clinical characteristics of patients with NHO are shown in Table 1 (Tab. 1). In one patient NHO was multifocal involving both hips and left elbow.

US examination showed a focal disorganization of muscle in the involved area, with loss of longitudinal muscular striation and presence of a heterogeneously hypoechoic mass with the characteristics of the classical “zone phenomenon” previously described in literature, in particular in the hip.
The zone phenomenon was always evident in NHO of the hip (2 patients) and appeared as an inner hypoechoic core surrounded by a ring of hyperechoic mineralized islands, with an outer hypoechoic zone adjacent to normal muscle (Fig. 1). PDUS demonstrates vascular signal (grade 2 in both patients) within mineralizing area and in outer hypoechoic area and SWA of vessels within NHO always showed RI<1. No vascular signal was observed in the central hypoechoic core. No synovitic intracapsular vascular signal was observed.

In NHO of knee (4 patients) the classical zone phenomenon was less evident. A heterogeneously hypoechoic mass was evident within insertional area of vastus medialis muscle and proximal enthesis of medial collateral ligament (Fig. 2a). In a case mild hyperechoic deposits were observed also within distal enthesis of medial collateral ligament. PDUS showed intense vascularisation inside the lesion (grade 3 in 3 patients, grade 2 in one) (Fig. 2b) and SWA of vessels within NHO always showed RI<1 (Fig. 2c).

In NHO of elbow (1 patient) only mild hyperechoic deposits in olecranic recess of the joint were observed and the zone phenomenon was not evident (Fig. 3). PDUS demonstrates vascular signal within mineralizing area (grade 1). In all the site SWA of vessels within NHO always showed RI<1.

Only hip and elbow NHO were associated with significant joint effusion (Fig. 1) but no synovitic intracapsular vascular signal was observed. In knee NHO joint effusion was always small.

The dynamic examination always showed a low compressibility of the hypoechoic areas during the application of a pressure with the probe.

In our case study only a NHO of the hip evolved within one year in complete ankylosis, while in the other cases an acceptable ROM was maintained.

**Discussions**
NHO is a complication of brain and spinal injury and its prevalence varies from 16% to 53% in traumatic patients. Scanty data are available about incidence of NHO in not-traumatic neurological disorders. A recent work showed 4% of incidence in a neurorehabilitation unit. Our data shows comparable results with a similar diagnostic algorithm.

According with literature hip, knee and elbow were the most frequently affected joints. Severe and rapid limitation of range of motion was the most common sign of NHO in our patients, while pain was not always detectable because of sensory deficits and/or concomitant severe aphasia. In knee and elbow a firm swelling was observed in the site on NHO within few days from diagnosis. In NHO of hip palpable mass was not appreciable because of the depth of joint.

In 4 patients AP, ESR and CRP were elevated in early stages of NHO and decreased after beginning of therapy. In 2 cases with small NHO of knee only ESR and CRP was elevated. Our data confirm the usefulness but incomplete sensitivity of these inexpensive investigation in diagnosis of NHO. In fact, as confirmed in previous works, if NHO formation is small, ALP levels may remain unchanged. Moreover, low specificity of these laboratory findings should be considered, in particular in critical ill patients (concomitant infection, tracheostomy, recent neurosurgery, pressure sores).

In all the cases plegia and muscular hypertonia or spasticity was present in the affected limbs. This risk factor is often reported in literature as cause of muscle hypoxia and increased risk of muscle tears from mobilization.

Our gray-scale US data support the highly specific pattern of “zone phenomenon” in NHO of the hip, while in other localizations differential diagnosis with arthritis, tumour and abscess could be more difficult.

In hips NHO were localized in a plane deep to the rectus femoris and superior to the coxo-femoral capsule, as recognized in previous MRI works. Iliopsoas muscle or iliopsoas bursa
seem the first involved sites. However in coxo-femoral joint an effusion was always observed. This effusion could be secondary to the adjacent intense inflammatory process.

In knees NHO involved vastus medialis fibers in its entheseal area and proximal fibrocartilaginous enthesis of medial collateral ligament. In our cases knee effusion was minimal, whereas a previous work reported joint effusion with synovial hypertrophy. In elbow NHO was evident in the olecranic recess, probably in medial head of triceps muscle or in olecranic bursa.

In our experience the low compressibility of lesions underneath the probe is a useful sign to diagnose NHO.

In our knowledge this is the first work in which PDUS was applied to the study of early NHO. Our data confirm that hypervascularization of mineralizing areas is a relevant diagnostic aspect of NHO lesions, as previously observed with angiographic studies. Moreover the flow pattern indicate the presence of low resistance vessel as reported in inflammatory neoangiogenesis. The inner core of early NHO appears as a relatively avascular area. Previous observations with MRI confirmed the strong ring enhancement of early HO after administration of Gadolinium-based contrast.

No flow signal was observed in synovial layer within adjacent joints. This can strengthen the hypothesis of a reactive and secondary joint effusion.

Medical management of NHO is controversial and supported with limited evidence. In our case study only a NHO of the hip evolved within one year in complete ankylosis. In our multifocal case therapy has been relatively effective in elbow but not in hips. Previous works reported different outcome after standardized therapy in various involved sites of the same patient. NHO in knee seems to have better evolution with respect to other sites.

This study has some limitations. The incidence of NHO in brain injured patients could be underestimated because we studied by imaging only sites with clinical signs or symptoms, so
subclinical NHO could be missed. Moreover, the time period of follow-up has been limited to about one year. However this diagnostic protocol has been used in previous studies and avoids the high costs of a screening imaging protocol.

Another limitation is the heterogeneity of the diagnosis of case series, but it is related to the neurorehabilitative setting of the study.

In conclusions, NHO is a frequent cause of reduction of ROM and secondary disability following severe acquired brain injury. As early detection of NHO and prompt starting of therapy are essential to contain related disability, bedside US seems a useful first-step diagnostic tool when clinical and/or laboratory findings induce suspicion of NHO.

References


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<tr>
<th>Sex, Age (years)</th>
<th>Neurologic injury (and clinical state)</th>
<th>site of NHO</th>
<th>NHO diagnosis (weeks from neurologic injury)</th>
<th>laboratory findings at NHO onset</th>
<th>PDUS grading</th>
<th>outcome after 1 year</th>
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<tr>
<td>1 F, 56</td>
<td>rupture of left middle cerebral artery arteriovenous malformation, neurosurgery for subdural hematoma (right hemiplegia and left hemiparesis with hypertonus, severe aphasia, PEG, no DVT or pressure sores)</td>
<td>right hip, left hip, left elbow</td>
<td>14 w ESR 75 mm/h, CRP 1.49 mg/dL, AP 715 mg/dL, bony IE 50.8 mcg/L</td>
<td>2 mild reduction of extension of left elbow, complete ankylosis of hips</td>
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<td>2 M, 41</td>
<td>post-hypoxic encephalopathy (vegetative state, bilateral hemiplegia with hypertonus, tracheostomy, PEG, bilateral DVT, no pressure sores)</td>
<td>left knee</td>
<td>12 w ESR 69 mm/h, CRP 1.1 mg/dL, AP 442 mg/dL, bony IE 9.2 mcg/L</td>
<td>3 acceptable ROM</td>
<td></td>
<td></td>
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<td>3 F, 68</td>
<td>head injury (left hemiplegia with hypertonus, no DVT or pressure sores)</td>
<td>left knee</td>
<td>18 w ESR 28 mm/h, CRP 2.79 mg/dL, AP 280 mg/dL</td>
<td>3 acceptable ROM</td>
<td></td>
<td></td>
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<tr>
<td>4 F, 72</td>
<td>right intracerebral hemispheric hemorrhage, decompressive craniectomy for high intracranial pressure (left hemiplegia with hypertonus, tracheostomy, PEG, no DVT or pressure sores)</td>
<td>left hip</td>
<td>15 w ESR 49 mm/h, CRP 4.75 mg/dL, AP 401 mg/dL</td>
<td>2 mild reduction of ROM</td>
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<td></td>
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<td>5 M, 40</td>
<td>head injury, decompressive craniectomy for high intracranial pressure (bilateral hemiparesis, tracheostomy, no DVT or pressure sores)</td>
<td>right knee</td>
<td>11 w ESR 26 mm/h, CRP 0.68 mg/dL, AP 121 mg/dL</td>
<td>3 acceptable ROM</td>
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<td>6 F, 76</td>
<td>subarachnoid hemorrhage for ruptured aneurysm of anterior communicating artery, endovascular selective embolization (bilateral hemiplegia with hypertonus, severe aphasia, tracheostomy, PEG, no DVT or pressure sores)</td>
<td>right knee</td>
<td>13 w ESR 73 mm/h, CRP 8.75 mg/dL, AP 103 mg/dL</td>
<td>2 mild reduction of extension of right knee</td>
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Table 1

Demographic and clinical characteristics of NHO patients.

ESR, erythrocyte sedimentation rate (normal values 2-25 mm/hour). CRP, C-reactive protein (normal values <0.5 mg/dL). AP, alkaline phosphatase (normal values 40-129 mg/dL for female, 35-104 mg/dL for male). bony IE, iso-enzyme of AP (normal values 3.8-22.4 microg/L). ROM, range of motion. DVT deep venous thrombosis. PEG, percutaneous endoscopic gastrostomy.
Figure 1. Sagittal longitudinal US scan of left hip (patient 1). The classical aspect of the “zone phenomenon” of HO was evident in iliopsoas muscle, with an inner hypoechoic core (curved arrow) surrounded by a ring of hyperechoic mineralized islands (arrowhead), and an outer hypoechoic zone adjacent to normal muscle. Hypoechoic effusion (*) is visible within coxo-femoral joint capsule.

170x102mm (75 x 75 DPI)
Figure 2a. Coronal transverse US scan of left knee over vastus medialis muscle (patient 2). A heterogeneously hypoechoic mass (between arrowheads) is evident within vastus medialis muscle (VMm). The cortical profile of femur appears regular.
Figure 2b. Coronal transverse US scan of left knee over vastus medialis muscle (VMm) (patient 2). PDUS demonstrates a vascular tree within the hypoechoic mass of HO (grade 3).
Figure 2c. Coronal transverse US scan of left knee over vastus medialis muscle (patient 2). PDUS and SWA demonstrates low resistance flow in HO hypoechoic mass, with RI 0.50. 170x138mm (75 x 75 DPI)
Figure 3. Coronal posterior longitudinal US scan of left elbow (patient 1). A hyperechoic mineralized mass is visible in medial side of olecranic recess (between harrowheads). PDUS demonstrates vascular signal within the mass (grade 1). O = olecranon.

81x72mm (75 x 75 DPI)