Author's response to reviews

Title: Acquired heterotopic ossification in hips and knees following encephalitis: case report

Authors:

Hong X Zhang (zhangxianghong2008@126.com)
Shuo Jie (csxhs@126.com)
Tang Liu (liutang1981@126.com)
Sheng X Zhang (liutang1981@126.com)

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Abstract

Heterotopic ossification (HO) is a potential complication following severe head injury, spinal injury, nontraumatic intracranial lesion and long-term coma. Post-encephalitis HO is rare and literature revealed that most of this rare cases are major with one or two anatomical regions affected. We present a 47-year-old man with HO in the bilateral hips and bilateral knees that prevented him from walking following after being attacked by encephalitis as the case study. The management of HO is controversial. After surgical excision, reconstruction of the medial collateral ligament and pharmacotherapy of Celecoxib after operation, he regained mobility of the joints. On review of X-ray, there was no recurrence of HO and no loose of rivets which were used in the reconstruction of medial collateral ligament. HO in the bilateral hip-joints and bilateral knee-joints associated with encephalitis have never been reported previously.

Keywords: Heterotopic ossification; Encephalitis; Hip; Knee

Introduction

Heterotopic ossification (HO) is a pathological process of lamellar bone formation in soft tissue outside of skeleton. HO occurs frequently after severe head injury, spinal injury, nontraumatic intracranial lesion and long-term coma. It severely restricts the movements of the major joints. However, there is a limited number of cases in the medical literature, where the condition affects one or two anatomical regions in association with encephalitis. The etiopathogenesis of HO is unknown and there is lack of consensus on treatment modalities. Report here is a rare case of periarticular HO in the bilateral hips and bilateral knees of 47-year-old man following encephalitis and 1 month in coma. After surgical excision, reconstruction of the medial collateral ligament and 200mg daily of Celecoxib for 8 weeks postoperatively, he regains mobility of the joints. To the best of our knowledge, this is the first report of such a rare case.

Case report

A 47-year-old man, with no past medical history, suddenly complained of headaches, without fever, vomiting and altered consciousness on February 10, 2012. Then he was admitted to the nearby clinic, but it was useless and the headache was aggravated, following hyperpyrexia. To strive for better treatment, then he was admitted to the superior hospital, and he was got into department of neurology. After admission, there were apparent cognitive deficits, which is named disorientation, short attention span, and his consciousness was disordered gradually which progressed to coma. A magnetic resonance imaging (MRI) of the brain was
unremarkable, and examination of cerebrospinal fluid and cerebrospinal fluid cultures were negative, so he was treated for presumed viral encephalitis. According the profile, result of blood test and imaging evidence, the patient was treated with antiviral therapy, antiepileptic therapy and empirical antibiotics in this period of coma. After this period of 30 days’ coma, his mental states and speech improved with vigorous and effective treatment, but the ambulation did not improved significantly. Therefore, he has difficulty with using of the lower extremities.

Frome then on, he consulted with several doctors from time to time, regarding the stiffness of both the hips and knees, but his condition was not improved. Ten months after the onset of the coma, in order to pursue natural movement, he came our department of orthopedics. Both his hips and knees were stiff, as the Table 1 below shows, and all other joints were normal.

The patient’s laboratory findings were normal except for a slight increase in erythrocyte sedimentation rate (ESR) (24mm/h; normal,0-15mm/h ). Radiographs of the pelvis showed para-articular HO on the interior aspect of both the femoral necks (Fig.1). Anterioposterior and lateral radiographs of knees(Fig.2) showed HO on the peripheral areas of knee-joint, especially on the interior. Lesions of four joints were also clearly showed in radiographs of the both lower extremities (Fig.3).

After admission, the patient and his family received pre-operation counseling, including the explanations of the available management options, expected outcome and possible complications. On December 5, 2012, he underwent the first operation: Excision of the heterotopic bone of both knees was performed. At surgery, an osteotome was used to excise the ossific mass in sufficient amount to free the joints, and the medial collateral ligaments of both knees had degenerative changed, therefore the reconstruction of the medial collateral ligament was applied. One months later, he underwent another surgery of excision of the heterotopic bone of both hips. After operation, the patient was given200mg daily of Celecoxib for 8 weeks postoperatively. Postoperative radiographs of both knees were showed that the most of heterotopic bone of both knees had been excised (Fig.4, 5). At the last follow-up visit, 13 months after the operation and 23 months after the coma, he had no pain and could walk independently, though he walked slowly. The range of motion improved, and the detailed information could be seen in above chart (Table 2). On review of X-ray, there was no recurrence of HO and no loose of rivets which were used in the reconstruction of medial collateral ligament.

Table 1: The comparison of rang of motion between pre-operation and postoperation

<table>
<thead>
<tr>
<th></th>
<th>flexion</th>
<th>extension</th>
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<tbody>
<tr>
<td></td>
<td>Pre-operation</td>
<td>13 months after the operation</td>
</tr>
<tr>
<td>Left hip</td>
<td>0°-25°</td>
<td>0°-85°</td>
</tr>
<tr>
<td>Right hip</td>
<td>0°-15°</td>
<td>0°-80°</td>
</tr>
<tr>
<td>Left knee</td>
<td>0°-15°</td>
<td>0°-100°</td>
</tr>
<tr>
<td>Right knee</td>
<td>0°-10°</td>
<td>0°-90°</td>
</tr>
</tbody>
</table>
Fig. 1 Preoperative radiographs of the pelvis shows para-articular HO on the interior aspect of both the femoral necks.

Fig. 2 Preoperative radiographs of anterioposterior and lateral radiographs of knees shows HO on the peripheral areas of knee-joints, especially on the interior.

Fig. 3 Preoperative radiographs of both lower extremities shows Lesions of four joints.

Fig. 4; Fig. 5 Postoperative radiographs of anterioposterior and lateral radiographs of knees shows no loose of rivets and no recurrence 13 moths after the excision of the ossific mass.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age and gender</th>
<th>Time of coma</th>
<th>The affected joints</th>
<th>Locations</th>
<th>Therapies</th>
<th>Consequences</th>
</tr>
</thead>
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| R | L | R | L |

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<p>| R | L | R | L |</p>
<table>
<thead>
<tr>
<th>Authors</th>
<th>Age</th>
<th>Gender</th>
<th>Duration</th>
<th>Location</th>
<th>Imaging Description</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tay et al (10)</td>
<td>26</td>
<td>Female</td>
<td>28 days</td>
<td>Bilateral hips</td>
<td>Image of CT showed: medial aspect of upper thighs</td>
<td>Surgery and radiotherapy</td>
<td>No recurrence and moderate gain in the range of motion</td>
</tr>
<tr>
<td>Jayasundara et al (5)</td>
<td>21</td>
<td>Male</td>
<td>35 days</td>
<td>Bilateral hips and right elbow</td>
<td>CT showed: anterior, posterior and lateral aspects of both hips, Radiograph of the pelvis showed: anteroposterior</td>
<td>Surgery and physiotherapy</td>
<td>No recurrence and have acceptable range of movements at the affected joints</td>
</tr>
<tr>
<td>Saito et al (21)</td>
<td>26</td>
<td>Female</td>
<td>40 days</td>
<td>Bilateral knees</td>
<td>CT showed: Large area of the left distal femur and small area of right knee</td>
<td>Surgery and 800mg daily of etidronate disodium</td>
<td>Slight recurrence occurred 3 weeks after surgery</td>
</tr>
<tr>
<td>An et al (4)</td>
<td>38</td>
<td>Female</td>
<td>13 months</td>
<td>Right shoulder and left elbow</td>
<td>Unknown</td>
<td>Excision, physical and diphosphonate postoperation</td>
<td>No recurrence and the range of motion improved markedly</td>
</tr>
<tr>
<td>Ours case</td>
<td>47</td>
<td>Male</td>
<td>1 month</td>
<td>Both hips and knees</td>
<td>interior aspect of both the femoral necks and the peripheral areas of knee-joints, especially on the interior.</td>
<td>Excision and 200mg daily of Celecoxib</td>
<td>No recurrence and walk independently</td>
</tr>
</tbody>
</table>

Table 2: A brief summary about patients associated with HO following encephalitis.

Discussion

HO is defined as the formation of mature lamellar in soft tissues that normally do
not ossify. After brain or spinal cord injury, trauma, neurologic disease or injuries, or hereditary disease, HO may occur. But HO following viral encephalitis is very rare. Our report demonstrates heterotopic bone arising from periarticular region of both hips and both knees in a patient who suffered 1 month prolonged coma following encephalitis. To the best of our knowledge, this is the first report of HO in both hips and both knees following encephalitis. And we make a simple chart (Table 2) below to show the distinctions between patients who suffered multiple-joint following encephalitis. The patient and his family received pre-operation counseling, and on December 5, 2012, he underwent the first operations. And we had removed sufficient ossific mass and reconstruct the medial collateral ligament, which is the significiation difference to other cases and it also can make the joint more stable, to free the both knee-joints. One months later, he underwent another surgery of excision of the heterotopic bone of both hips. After operation, the patient was given medical treatment of Celecoxib. He had no recurrence of HO and no loose of rivets for up to 13 months after the surgery, with an acceptable range of movements and showed good short-term outcome.

The mechanism and pathophysiology, which can lead to HO, is still not fully understood. The study showed that primitive mesenchymal cells differentiate into osteoblasts which would lead to HO and the origin of these mesenchymal cells and the stimulus are poorly understood. Urist et discovered that demineralized bone matrix can induce the formation of HO, and they were also presented bone morphogentic protein is the true inductor. And Ho SSW et al, recently, put forward that Prostaglandin E2 is a transmitter to promote the original cell differentiation. Chalmers J et al proposed that following three requirements are necessary for HO, including: inducing agent, osteogenic precursor cell and an environment which is permissive to osteogenesis. Therefore, it is clear that further studies for the mechanism and pathophysiology of HO are required. Although the pathogenetic mechanism of HO remains unclear, functional immobility has been reported to be a risk factor. It is also difficult to accurately ascertain when the HO began, as the subject has no specificity. Atypical early clinical performance of HO are the causes of hard distinction from cellulitis, osteomyelitis, thrombophlebitis and tumor. In aspect of biochemical markers, alkline phosphatase (ALP) have some certain clinical significance of early diagnosis of HO, but ALP has no specificity. Glrlnd DE et al had told us that prolonged coma, mechanical ventilation, spasticity and limited extremity movements may be the initiators of neurogenic HO. Therefore, it is difficult to determine onset of HO following encephalitis in using biochemical markers. HO at different stages shows different imaging features. Someone thought MRI is the best effective methods for the diagnosis of early ectopic ossification, X-ray and CT can be used for review. Practice literature reports told us that X-ray could not discover HO until 4-6 weeks later. While some literature showed that the most sensitive imaging modality for early detection of HO is three-phase bone scintigraphy which can also monitor the metabolic activity and degree of maturity of HO. And the researches also told us that none of the available prophylactic measures would affect the outcome of HO once the process has begun.
Numerous treatment options, including pharmacotherapy (such as: non-steroidal anti-inflammatory drugs (NSAIDs), disodium etidronate (EHDP) et al), motortherapy, radiotherapy, surgical therapy et al, are available, but deciding which modality to pursue is dependent on a detailed and accurate assessment of the disease process. NSAID was recognized the most effective drugs to prevent the formation of HO after operation of acetabulum fracture. Coventry MB et al made a research with patients who had total hip arthroplasty, and they believed that radiation aids in the prevention of formation of ectopic bone. As increasing the range of movements at the joints and improving function and quality of life were most patients’ purposes, surgery was also a choice among treatments. However, for surgery, when is the best time to do the surgery? Many researches had told that it need to wait the heterotopic bone matured. Garland et al suggested that it require 18-month before surgical excision in order to allow the bone to mature. And most scholars recommended a minimum wait of 1 year after ectopic bone formation ahead of surgical excision.

Though the maturity of heterotopic bone is difficult to evaluate, it is important to prevent the high recurrence rate relevant to excision of immature ectopic bone. Recurrence is also an important complication of HO which we should consider after excision. The risk of recurrence is also higher in patients undergoing multiple operations sequentially and it found that the risk of recurrence HO was high if the three or more joints were involved. So to free the joint, it is necessary to remove sufficient ossific mass, but complete excision is not necessary. Active exercises can begin after the first postoperative week.

In conclusion, further studies for the early diagnosis and optimal managements of HO following encephalitis are required. When a patient develops decreased joint range of motion, differential diagnosis should be taken into consider. And different patient should be managed with a different appropriated protocol based on the institutional experience.

Reference


