**Author's response to reviews**

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

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**Version:** 8  **Date:** 20 August 2014

**Author's response to reviews:** see over
Dear Sir or Madam:

Thank you for your attention to our article.

Reviewer's report (1)

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

Version: 7 Date: 22 March 2014

Reviewer: Sergiu Botolin

Reviewer's report:

1. Interesting and actual topic.

Answer: Thank you.

2. Very poor English. Multiple grammatical mistakes. Needs extensive

Answer: Thank you. We have asked a native-English speaker to help us copyedit our manuscript.

3. The problem of heterotopic ossification was recently in great detail by Botolin et al in their article which addresses many of the discussion points used by the present authors and as such deserves to be cited in this work.

Answer: Thank you. We have re-read some literature about the problem of heterotopic ossification which was recently in great detail discussed, and we have cited some of them in our manuscript.
1. We added: “Botolin et al (14), also put forward that both the reaming debris and the extent of traumatic intraoperative injury to the surrounding soft tissues at the operative site play important roles in the development of HO after antegrade reamed femoral IMM in their case study. Several studies also have demonstrated that the low-oxygen tension (15) and neurotransmitters are involved in the process of HO formation.” in the paragraph beginning “The mechanism and pathophysiology, which....”.

2. We added: “Once these conditions are meet, mesenchymal cells are recruited, which then proliferate and differentiate into chondrocytes and/or osteoblasts, and ultimately lead to ectopic bone formation (3)” ; “Gannon FH et al discovered that inflammation first occurs in response to stimulations, including surgery, trauma and viral illnesses (9).“ and “Bidner SM et al (10) proposed that failure of control in the immune system, central nervous system or indigenous inflammatory response lead to the release of inducing agents, resulting in HO formation.” in the paragraph beginning “The mechanism and pathophysiology which....”.

3. We added: “Peterson JR (23) et al also suggested that Roman Spectroscopy allowed for detection of HO formation as early as 5 days in mice following a burn injury. ” in the new paragraph beginning “It is also difficult to ascertain when the HO formation begins accurately...”.

4. We added: “Garland DE recommended that HO resection should be performed at different time intervals according to the HO aetiology: traumatic HO
should be resected at 6-9 months, spinal cord injury at 1 years and traumatic brain injury HO at 1.5 years (29). “, in the new paragraph beginning “ However, it is difficulty to decide when the best time is for the revision surgical resection of HO?.....”.

5. We added: “Botolin et al supposed that diligent intraoperative care of the soft tissues and copious fluid irrigation with saline in the procedure of revision surgery appear to decrease the recurrence rate (14)” in the new paragraph beginning “ However, it is difficulty to decide when the best time is for the revision surgical resection of HO?.....”.


Reviewer's report (2)

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

Version: ? Date: 20 July 2014

Reviewer: Shu-Guang Gao

Reviewer's report:

1. This needs improvement in English grammar and sentence use.

Answer: Thank you. We have asked a native-English speaker to help us copyedit our manuscript, and we have checked the content of our manuscript carefully.

2. Please add figure to the postoperative range of both knees.
Answer: Thank you. We have added the figures of “Fig.6, Fig.7” to show the postoperative range of both knees.

Fig.6 & Fig.7 Postoperative radiographs of knees shows no loose of rivets and no recurrence 18 months after the excision of the ossific mass, and the passive range of motion of knees had significantly improved.

3. This statement needs some discussion e.g. its clinical significance.

Answer: Thank you. We have re-read some literature about heterotopic ossification, and we have made a more extensive discussion than before in our manuscript.

Such as:

1. In clinical significance, we changed the sentence “Further studies for the early diagnosis and optimal managements of HO following encephalitis are required.” in the paragraph of ‘Conclusion ’ to “Daily functions of heterotopic ossification patients can be hampered by pain, inflammation, reduced mobility, the loss of normal posture, and other complications. Therefore, to fully understand the pathogenesis of HO and to
determine its risk factors, root causes and preventability of this potentially detrimental complications, further study is required. Different patient should be managed with a different appropriated protocol based on the risk of individual patient and the institutional experience.”.

2. We added : “Gannon FH et al discovered that inflammation first occurs in response to stimulations, including surgery, trauma and viral illnesses (9). Inflammatory and skeletogenic signaling pathways are also supposed to play critical roles in HO formation. Bidner SM et al (10) proposed that failure of control in the immune system, central nervous system or indigenous inflammatory response lead to the release of inducing agents, resulting in HO formation.” after the sentence beginning “Many studies showed that primitive mesenchymal cells differentiate into osteoblasts which....” in the paragraph beginning “ The mechanism and pathophysiology which.....”.

3. We added : “ Once these conditions are meet, mesenchymal cells are recruited, which then proliferate and differentiate into chondrocytes and/or osteoblasts, and ultimately lead to ectopic bone formation (3). Botolin et al (14), also put forward that both the reaming debris and the extent of traumatic intraoperative injury to the surrounding soft tissues at the operative site play important roles in the development of HO after antegrade reamed femoral IMM in their case study. Several studies also have demonstrated that the low-oxygen tension (15) and neurotransmitters are involved in the process of HO formation. Grlrland DE et al (16) told us that prolonged coma, mechanical ventilation, spasticity and limited extremity movements may be the
initiators of neurogenic HO. ” after the sentence beginning “ Chalmers J (13) et al proposed that the following three requirements are necessary for HO formation, namely: inducing agent, osteogenic....” in the paragraph beginning “ The mechanism and pathophysiology which.....”.

4. We added : “ Without early detection or intervention, progression of HO can lead to severe long-term effects, including restricted joint mobility, severe pain, and nerve entrapment.” after the sentence beginning “Atypical early clinical performance of HO are the causes of....” in the new paragraph beginning“ It is also difficult to ascertain when the HO formation begins accurately,.....“.

5. We added : “ Although radiographic techniques such as computed tomography and magnetic resonance image provide high detailed anatomic representation of late stage HO, these modalities cannot detect early stages of HO. In summary, current imaging modalities, including CT, MRI and three-phase bone scintigraphy through helpful late diagnosis are inadequate to help clinicians detect early HO development. The formation of HO begins within days to weeks of the inciting event. The disease has already spread beyond the point where it can be treated and impeded with oral medications, once visible through these current techniques.” after the sentence beginning “ While some literature show that the most sensitive imaging modality for early detection of HO is....” in the new paragraph beginning “ It is also difficult to ascertain when the HO formation begins accurately,.....“.

6. We added : “ Therefore, a urgent need exists to improve the current diagnostic modalities for HO which are inadequate to diagnose and intervene on HO at early
time-points. Many researches showed that Roman Probe propelled non-invasive, transcutaneous evaluation of heterotopic bone formation. Petrson JR (23) et al also suggested that Roman Spectroscopy allowed for detection of HO formation as early as 5 days in mice following a burn injury. Hence, we should try hard to develop novel screening techniques to visualize and detect the onset and progression of HO with high sensitivity and specificity.

"That is to say, none of the available prophylactic measures would affect the outcome of HO once the process has begun (22)." in the new paragraph beginning "It is also difficult to ascertain when the HO formation begins accurately.....”.

7. We added :“Garland DE recommended that HO resection should be performed at different time intervals according to the HO aetiology: traumatic HO should be resected at 6-9 months, spinal cord injury at 1 years and traumatic brain injury HO at 1.5 years (29). Serum alkaline phosphatase (ALP) is an important factor we should use to determine the timing of HO resection." after the sentence beginning “And most scholars recommended a minimum wait of 1 year after.....” in the new paragraph beginning “However, it is difficulty to decide when the best time is for the revision surgical resection of HO?....”.

8. We added : “In summary, as major treatment options discussed above have negative side effects to some extent, it is important to evaluate the risk of individual patients, and provide safe and effective treatments for them.” in the last paragraph of ‘Discussion’.
Dear Sir or Madam,

Thank you again.

This email of cover letter includes email attachment of the corrections of our manuscript. Following is the detail of our changes.

1. In segment of “Abstract”

   About “Background”:

   1. We changed the sentence of “Heterotopic ossification (HO) is a potential complication following severe head injury, spinal injury, nontraumatic intracranial lesion and long-term coma.” to “Heterotopic ossification (HO) is a rare and potentially detrimental complication of soft-tissue trauma, amputations, central nervous system injury (traumatic brain injuries, spinal cord lesions, tumors, encephalitis), vasculopathies, arthroplasties and burn injury, characterized by lamellar bone growth in non-osseous tissues such as the muscle and the joint capsule.”.

   2. We changed the sentence of “Post-encephalitis HO is rare and literature revealed that most of this rare cases are major with one or two anatomical regions affected.” to “Heterotopic ossification associated with encephalitis is rare and the occurrence of excessive, symptomatic heterotopic ossification around bilateral hips and bilateral knees is rarely described in the literature.”

   About “Case presentation”:
1. We deleted the word of “following” in the sentence beginning “We present a 47-year-old man with HO in the bilateral hips and bilateral knees that ....”.

2. We changed the sentence of “The management of HO is controversial.” to “He developed severe pain and significantly impaired range of motion of bilateral hips and bilateral knees. Research so far revealed that the management of HO is controversial.”.

3. We changed the sentence of “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.” to “After requiring revision surgery resection of heterotopic ossification, reconstruction of the medial collateral ligament and adjunctive pharmacotherapy of 200mg Celecoxib for 8 weeks after operation, he regained mobility of his joints. On review of X-ray, there was no recurrence of HO and no loosening of rivets which were used in the reconstruction of medial collateral ligament.”.

About “Conclusion”:

1. We added the sentence of “Daily functions of heterotopic ossification patients can be hampered by pain, inflammation, reduced mobility, the loss of normal posture and other complications.” after the sentence beginning “Heterotopic ossification in the bilateral hip joints and bilateral knee joints associated with ....”.

2. We changed the sentence of “Further studies for the early diagnosis and optimal managements of HO following encephalitis are required. And different patient should be managed with a different appropriated protocol based on the risk of individual
patient and the institutional experience. ”

Further studies of presumptive root causes, the early diagnosis, preventability and optimal therapeutic measures for heterotopic ossification following encephalitis are required. Different patient should be managed with different appropriated protocol based on the risk of individual patient and the institutional experience. “.

2. In segment of “Background”

1. We changed the sentence of “It severely restricts the movements of the major joints. “ to “However, the occurrence of excessive, symptomatic heterotopic ossification around bilateral hips and bilateral knees is rarely described in the literature. Daily functions of HO patients can be hampered by the loss of normal posture, pain, inflammation, reduced mobility, formation of pressure ulcers, deep venous thrombosis, and other complications (3). “.

2. We changed the sentence of “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(3). “ in the paragraph of “Background” to “Also 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 (4). “
3. **In segment of “Case presentation”**

1. We changed the sentences of “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. “ in the paragraph beginning “A 47-year-old man, with no past medical history, suddenly... “ to “ He was admitted to a nearby clinic, but it was useless and the headache got aggravated, following hyperpyrexia. To strive for better treatment, he got admitted into the neurology department of a superior hospital. After admission, there were apparent cognitive deficits: namely: disorientation, short attention span, and gradual disordered consciousness which progressed into coma. “ .

2. We changed the sentence of “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.“ in the paragraph beginning “A 47-year-old man, with no past medical history, suddenly... “ to “ A magnetic resonance imaging (MRI) of the brain was unremarkable. Examination of cerebrospinal fluid and cerebrospinal fluid cultures were negative, so he was then treated for presumed viral encephalitis. “ .

3. We changed the sentence of “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 of 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’ in the paragraph beginning “A 47-year-old man, with no past medical history, suddenly... “ to “According to the profile, results of blood test and imaging evidence, the patient was treated with antiviral therapy, antiepileptic therapy and empirical antibiotics within 30 days period of coma. After this period of 30 days of coma, his mental state and speech improved with vigorous and effective treatment, but the ambulation did not improve significantly. Therefore, he had difficulty using his lower extremities.”.

4. We changed the sentence of “From 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.” in the paragraph beginning “From then on, he consulted with...” to “From then on, he consulted with several doctors from time to time, regarding the stiffness of both the hips and knees, but the condition of his lower extremities did not improve.”.

5. We changed the sentence of “Ten months after the onset of the coma, in order to pursue natural movement, he came to our department of orthopedics. Both his hips and knees were stiff, as the Table 1 below shows, and all other joints were normal.” in the paragraph beginning “From then on, he consulted with...” to “Ten months after the onset of the coma, he came to our department of orthopedics in order to pursue natural movement. Both hips and knees were stiff and the clinical evaluation revealed the
following passive ranges of motion of hips and knees as showed in the Table 1 below. All other joints were normal. “.

6. We deleted the word of “the” in the sentence of “Radiographs of the pelvis showed para-articular HO on the interior aspect of both the femoral necks (Fig.1). “ and the sentence of “Anterioposterior and lateral radiographs of knees (Fig.2) showed HO on the peripheral areas of knee-joints, especially on the medial. Lesions of four joints were also clearly showed in radiographs of the both lower extremities (Fig.3) “, in the paragraph beginning “The patient’s laboratory findings were... “.

7. We added the word of “to our institution” in the sentence beginning “After admission,..... “ in the paragraph beginning “After admission to our institution, the patient and... “.

8. We added the sentence of “After extensive discussion of the risks and benefits of revision surgical excision of HO resection and concomitant peri-operative pharmacotherapy of Celecoxib for decreasing the risk of HO recurrence, the patient and his family agreed to proceed with the procedure as discussed. ” after the sentence beginning “ After admission to our institution, the patient and his family received ....” in the paragraph beginning “After admission to our institution, the patient and... “.

9. We changed the word of “excision” to “Revision surgical excision” in the sentence beginning “On December 5, 2012, he underwent the first operation.....“.

10. We changed the sentence of “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."

11. We added the sentence of "The patient tolerated the surgical procedures well.

12. We changed the sentence of "After operation, the patient was given 200mg daily of Celecoxib for 8 weeks postoperatively. " to "After operation, the patient was given 200mg Celecoxib orally once a day for a total of 8 weeks postoperatively. ".

13. We changed the sentence of "Postoperative radiographs of both knees were showed that the most of heterotopic bone of both knees had been excised (Fig.4&Fig.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. " to "Postoperative radiographs of both knees showed that most of heterotopic bone of both knees had been excised (Fig.4&Fig.5). At the last follow-up visit, 18 months after the operation (is 28 months after the coma) , he had no pain and could walk independently."
“After admission, the patient and his family received...” to “The passive range of motion of hips and knees had significantly improved and the detailed information can be seen in above chart (Table 1).”.

15. We changed the sentence of “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.” in the paragraph beginning “After admission, the patient and his family received...” to “On review of X-ray, there was no recurrence of HO and no loosening of rivets used in the reconstruction of medial collateral ligament (Fig.6 & Fig.7).”.

4. In segment of “Discussion”

1. We changed the sentence of “HO is defined as the formation of mature lamellar in soft tissues that normally do not ossify.” to “HO is a rare and potentially detrimental complication of soft-tissue trauma, amputations, central nervous system injury (traumatic brain injuries, spinal cord lesions, tumors, encephalitis) (5,6), vasculopathies, arthroplasties and burn injury, characterized by lamellar bone growth in non-osseous tissues such as the muscle and the joint capsule.”

2. We changed the sentence of “But HO following viral encephalitis is very rare(4).” to “HO associated with viral encephalitis is very rare (7). The occurrence of excessive, symptomatic heterotopic ossification around bilateral hips and bilateral knees is rarely described in the literature. “.

3. We added the words of “Under reviewing literature” and changed the word of “make” to “made” in the sentence beginning “And we make a simple chart (Table 2).”
below to show the distinctions between patients who suffered multiple-joint following encephalitis. “ after the word of “ And... “.

4. We added the sentences of “ Daily functions of heterotopic ossification patients can be hampered by pain, inflammation, reduced mobility, the loss of normal posture, and other complications (3). Research so far reveal that the management of HO is controversial. As supported by the successful outcome in the present study, we recommend considering HO resection in conjunction with peri-operative pharmacotherapy of Celecoxib. In our current case study, “ after the sentence beginning “ And under reviewing literature, we make a simple chart (Table 2) below to show .... “ in the paragraph beginning “ HO is a rare and potentially detrimental complication of soft-tissue trauma, .....“.

5. We changed the sentence of “ 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 signification difference to other cases and it also can make the joint more stable, to free the both knee-joints.“ in the paragraph beginning “ HO is a rare and potentially detrimental complication of soft-tissue trauma, .....“, to “ the patient suffered stiffness of hips and knees and his family received pre-operation counseling, of which on December 5, 2012 he underwent the first operations. In order to free the both knee joints, We removed sufficient ossific mass and reconstructed the medial collateral ligament. This is the significant difference to other reported cases in literature which can also make the joint more stable. “.
6. We changed the sentence of “After operation, the patient was given medical treatment of Celecoxib.” in the paragraph beginning “HO is a rare and potentially detrimental complication of soft-tissue trauma, .....“, to “The patient tolerated the surgical procedure well. After operation, the patient was given medical treatment of 200mg Celecoxib orally once a day for a total of 8 weeks.”.

7. We changed the sentence of “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.” in the paragraph beginning “HO is a rare and potentially detrimental complication of soft-tissue trauma, .....“, to “He had no recurrence of HO and no loose rivets for 18 months after the surgery with a significantly improved ranges of motion of hips and knees described in detail above.”.

8. We changed the sentence of “The mechanism and pathophysiology, which can lead to HO, is still not fully understood.” in the paragraph beginning “The mechanism and pathophysiology, which can...“ to “The mechanism and pathophysiology which can lead to HO formation, is still not fully understood. And molecular mechanisms of HO have not been fully elucidated.”.

9. We changed the word “poorly” to “poor” in the sentence beginning “Many studies showed that primitive mesenchymal cells differentiate into...“

10. We added the sentences of “Gannon FH et al discovered that inflammation first occurs in response to stimulations, including surgery, trauma and viral illnesses (9). Inflammatory and skeletogenic signaling pathways are also supposed to play critical roles in HO formation. Bidner SM et al (10) proposed that failure of control in
the immune system, central nervous system, or indigenous inflammatory response lead
to the release of inducing agents, resulting in HO formation.

Many studies showed that primitive mesenchymal cells differentiate into
osteoblasts which...

The mechanism and pathophysiology which can...

11. We changed the sentences of “Urist(6) et discovered that demineralized bone
matrix can induce the formation of HO, and they were also presented bone
morphogenic protein as the true inductor. And Ho SSW (7) et al, recently, put forward
that Prostaglandin E2 is a transmitter to promote the original cell differentiation.
Chalmers J (8) 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.

12. We added the sentences of “Once these conditions are met, mesenchymal
cells are recruited, which then proliferate and differentiate into chondrocytes and/or
osteoblasts, and ultimately lead to ectopic bone formation (3). Botolin et al (14), also
put forward that both the reaming debris and the extent of traumatic intraoperative injury to the surrounding soft tissues at the operative site play important roles in the development of HO after antegrade reamed femoral IMM in their case study. Several studies also demonstrated that the low-oxygen tension (15) and neurotransmitters are involved in the process of HO formation. Girland DE et al (16) told us that prolonged coma, mechanical ventilation, spasticity and limited extremity movements may be the initiators of neurogenic HO. “after the sentence beginning “Chalmers J (13) et al proposed that following three requirements are necessary for HO formation, namely:.....“ in the paragraph beginning “The mechanism and pathophysiology which can... “.

13. We changed the sentences of “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 (9). “in the paragraph beginning “The mechanism and pathophysiology, which can... “. Although the pathogenetic mechanism of HO remains unclear, functional immobility has been reported to be a risk factor (17). Therefore, it is obvious that further studies for the mechanism and pathophysiology of HO are required. “.

14. We changed the sentences of “It is also difficult to accurately ascertain when the HO began, as the subject has no specificity (10). “in the new paragraph beginning “It is also difficult to ascertain when does the HO formation begin accurately, because.... “. It is also difficult to ascertain when the HO formation begins accurately, because the subject of HO formation has no specificity (18) and lacks a
reliable method for early diagnosis “.

15. We added the sentence of “Without early detection or intervention, progression of HO can lead to severe long-term effects, including restricted joint mobility, severe pain, and nerve entrapment. “ after the sentence beginning “Atypical early clinical performance of HO are the causes of.... “ in the new paragraph beginning “ It is also difficult to ascertain when does the HO formation begin accurately, because.... “.

16. We changed the word of “ In aspect of “ to “ In the aspect of “ in .the sentence beginning “ In aspect of biochemical markers, alkline phosphatase (ALP) have... “

17. We changed the sentences of “ 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 (13). 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 (11,14). “ in the paragraph beginning “ It is also difficult to ascertain when the HO formation begins ...“ to “ Therefore, it is difficult to determine the onset of HO, including HO following encephalitis in using biochemical markers. HO at different stages shows different imaging characteristics. Someone thought magnetic resonance imaging (MRI) is the best effective method for the diagnosis of early ectopic ossification, whiles X-ray and computed tomography (CT)
can be used for review. Practice literature reports tell us that X-ray cannot discover HO until 4-6 weeks later (20). While some literature show 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 (19,21). “

18. We added the sentence of “Although radiographic techniques such as computed tomography and magnetic resonance image provide high detailed anatomic representation of late stage of HO, these modalities cannot detect early stages HO. In summary, current imaging modalities, including CT, MRI and three-phase bone scintigraphy, through helpful in late diagnosis, are inadequate to help clinicians detect early HO development. The formation of HO begins within days to weeks of the inciting event. The disease has already spread beyond the point where it can be treated and impeded with oral medications, once visible through these current techniques.” after the sentence beginning “While some literature show that the most sensitive imaging modality for early detection of HO is three-phase....” in the new paragraph beginning “It is also difficult to ascertain when does the HO formation begin accurately, because.... “.

19. We added the sentence of “Therefore, an urgent need exists to improve the current diagnostic modalities for HO which are inadequate to diagnose and intervene on HO at early time-points. Many researches showed that Roman Probe propelled non-invasive, transcutaneous evaluation of heterotopic bone formation. Petronson JR (23) et al also suggested that Roman Spectroscopy allowed for detection of HO formation as early as 5 days in mice following a burn injury. Hence, we should try
hard to develop novel screening techniques to visualize and detect the onset and progression of HO with high sensitivity and specificity. “after the sentence beginning” That is to say, none of the available prophylactic measures would affect the outcome of HO once.... “in the new paragraph beginning” It is also difficult to ascertain when the HO formation begins accurately, because.... “.

20. We changed the sentence of “Numerous treatment options, including pharmacotherapy (such as: non-steroidal anti-inflammatory drugs (NSAIDs)(16), 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.” in the paragraph beginning “ Numerous treatment options, including pharmacotherapy......” to “Numerous treatment options, including pharmacotherapy (such as: non-steroidal Anti-inflammatory drugs (NSAIDs) (24), disodium etidronate (EHDP) et al), motortherapy, radiotherapy, surgical therapy et al, are available but decision on which modality to choose depends on a detailed and accurate assessment of the disease process.”

21. We changed the words of “NSAID was recognized “ in the sentence beginning “NSAID was recognized the most effective drugs to prevent the formation“ to “NSAID was recognized as“.

22. We added the sentences of “Most doctors agree that indomethacin is the best choice among NSAIDs not only prevent HO but also slows down the process of HO development. However, the application of NSAIDs is relatively limited, for its adverse drug reaction such as gastrointestinal ulceration, decreased platelet
aggregation, and renal toxicity. “after the sentence of “ NSAIDs were recognized as the most effective drugs to prevent the formation of HO after operation of acetabulum fracture (25).“ in the paragraph beginning “Numerous treatment options, including ...“. 

23. We changed the words of “ Coventry MB(18) et al made a research “ in the sentence beginning” Coventry MB (26) et al conducted a research....“ to “ Coventry MB (26) et al conducted a research “.

24. We added the sentences of “ However, the potential side effect that we should consider is carcinogenesis. Despite the risk that it can trigger another round of HO, surgery remains the only treatment option to date once bone tissue has formed. “after the sentence beginning “ Coventry MB (18) et al conducted a research with patients who had HO following total hip arthroplasty....” in the paragraph beginning “Numerous treatment options, including .. “.

25. We changed the sentences of “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. “ in the paragraph beginning “Numerous treatment options, including .. “ to “ To increase the range of movements of the joints and improve function and quality of life surgery was a good choice among treatments. Therefore, we choose the method of revision surgical resection in our case study. “

26. We changed the sentences of “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. “ in the new paragraph beginning “However, it is difficulty to decide when....
“to” However, it is difficulty to decide when the best time is for the revision surgical resection of HO? Many researches have indicated that there is a need to wait for the heterotopic bone to matured before the procedure is undertaken.“.

27. We added the sentences of “Garland DE recommended that HO resection should be performed at different time intervals according to the HO aetiology: traumatic HO should be resected at 6-9 months, spinal cord injury at 1 years, and traumatic brain injury HO at 1.5 years (29). Serum alkline phosphatase (ALP) is an important factor we should use to determine the timing of HO resection.” after the sentence beginning “And most scholars recommended a minimum wait of 1 year after ectopic bone....” in the new paragraph beginning “However, it is difficulty to decide when....“.

28. We changed the sentence of “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 (22) and it found that the risk of recurrence HO was high if the three or more joints were involved (19). “ in the paragraph beginning “However, it is difficulty to decide when....“ to “Recurrence is also an important complication of HO which should be considered after excision. The risk of recurrence is higher in patients undergoing multiple operations sequentially (31) and it is found out that the risk of recurrence HO was high if the three or more joints were involved (27). “.

29. We added the sentences of “Botolin et al supposed that diligent intraoprative care of the soft tissues and copious fluid irrigation with saline in the procedure of
revision surgery appear to decrease the recurrence rate (14).“ after the sentence beginning “The risk of recurrence is higher in patients undergoing multiple operations sequentially (31) and .... ” in the new paragraph beginning “ However, it is difficulty to decide when .... “.

30. We changed the sentences of “ 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 (19). “ in the new paragraph beginning “However, it is difficulty to decide when is.... “ to “ In order to free the stiffness in joint because of HO, it is necessary to remove sufficient ossific mass, but complete excision is not necessary. And to decrease the recurrence rate of HO, active exercises should begin after the first postoperative week (27). “.

31. We changed the sentences of “ 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.“ in the last paragraph of “Discussion” to “ In summary, as major treatment options discussed above have negative side effects to some extent, it is important to evaluate the risk of individual patients, and provide safe and effective treatments for them. Further studies for the mechanism and pathophysiology, the early diagnosis and optimal managements of HO following encephalitis are required. “.
5. In segment “Conclusion”

We changed the paragraph of “HO in the bilateral hip joints and bilateral knee joints associated with encephalitis have never been reported previously. Further studies for the early diagnosis and optimal managements of HO following encephalitis are required.” in “Conclusion” to “Heterotopic ossification in the bilateral hip joints and bilateral knee joints associated with encephalitis have never been reported previously. Daily functions of heterotopic ossification patients can be hampered by pain, inflammation, reduced mobility, the loss of normal posture, and other complications. Therefore, to fully understand the pathogenesis of HO and to determine its risk factors, root causes, and preventability of this potentially detrimental complications, further study is required. Different patient should be managed with different appropriated protocol based on the risk of individual patient and the institutional experience.”.

6. In segment of “Reference”


7. In segment of “Table”

In order to add figure to the postoperative range of both knees, the patient was followed up again. At this follow-up visit, 18 months after the operation (is 28 months after the coma), due to actively functional rehabilitation, the passive range of motion of knees and hips had improved compared to the last thirteen-months follow up. And the detailed information about this eighteen-months follow up were added into Table 1.

Table 1: The comparison of range of motion between pre-operation and post-operation

<table>
<thead>
<tr>
<th></th>
<th>flexion</th>
<th>extension</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-operation 13 months 18 months</td>
<td>Pre-operation 13 months 18 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>after the after the after the operation operation operation</td>
<td>operation operation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>flexion deformity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0°-25° 0°-85° 0°-110°</td>
<td>0°-15° 0°-10° 0°-15°</td>
<td></td>
</tr>
<tr>
<td>Left hip</td>
<td>0°-15° 0°-80° 0°-105°</td>
<td>0°-15° 0°-10° 0°-10°</td>
<td></td>
</tr>
<tr>
<td>Right hip</td>
<td>0°-15° 0°-100° 0°-125°</td>
<td>0° 0°</td>
<td></td>
</tr>
<tr>
<td>Left knee</td>
<td>0°-10° 0°-90°, 0°-127°</td>
<td>0° 0°</td>
<td></td>
</tr>
<tr>
<td>Right knee</td>
<td>0°-10° 0°-90°, 0°-127°</td>
<td>0° 0°</td>
<td></td>
</tr>
</tbody>
</table>

8. In segment of “Figure”

In order to add figure to show the postoperative range of both knees, We added “Fig.6” and “Fig.7”.

“Fig.6” and “Fig.7”.
Fig. 6 & Fig. 7 Postoperative radiographs of knees shows no loosening of rivets and no recurrence 18 moths after the excision of the ossific mass, and the passive range of motion of knees had significantly improved.

9. In segment of “Figure Legends”

We added “Fig. 6 & Fig. 7 Postoperative radiographs of knees shows no loosening of rivets and no recurrence 18 moths after the excision of the ossific mass, and the passive range of motion of knees had significantly improved.”

Yours sincerely,

Dr T Liu