Author's response to reviews

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

Authors:

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Author's response to reviews:

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.

   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 discussed 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.

   Such as:
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: 7 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

Fig.6 & Fig.7 Postoperative radiographs of knees shows no loose 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.

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.
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. Glrland 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. Petron 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 of “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.

Yours sincerely,

Dr T Liu