Author's response to reviews

Title: Pathological fracture of the femur in Alagille syndrome treated with low-intensity pulsed ultrasound stimulation and Ilizarov ring fixator

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Author's response to reviews: see over
Pathological fracture of the femur in Alagille syndrome that was treated with low-intensity pulsed ultrasound stimulation and an Ilizarov ring fixator: a case report

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Version: 2

Authors’ response to reviewers: see below
May 28, 2014
The Biomed Central Editorial Team

MS: 9481321981221407 (Pathological fracture of the femur in Alagille syndrome treated with low-intensity pulsed ultrasound stimulation and Ilizarov ring fixator, by Dr Koji Nozaka et al.)

Thank you for consideration of our manuscript for publication in *BMC Musculoskeletal Disorders*.

We have reviewed our manuscript according to the reviewers’ comments. Our replies to the reviewers’ comments are provided below.

**Reviewer #1 (Dr Peter Turnpenny)**

Major compulsory:

Much of the written text under 'Conclusions' constitutes 'Discussion' material and the paper should be reorganised accordingly. I have highlighted this in the attached pdf which includes comments added to the paper.

- Conclusions→Discussion (page 7, line 17).

Minor essential:

These can be found in my comments boxes in the attached file. The way some items are expressed needs to conform to a standard, relating to English, description of the syndrome, or centile values for the measurement parameters, for example.

Abstract

Background

- aplasia→Hypoplasia or paucity would be better

- We do not say there is malformation of the facies. It is better to simply say: “... and abnormal facies.”

  *We appreciate the reviewer’s comment on this important issue. According to the reviewer’s comment, we have changed this sentence to “Alagille syndrome is a multisystem disorder, which is characterized by hypoplasia of the intrahepatic bile ducts, malformations of the cardiovascular system, eyes, and vertebral column, and abnormal facies.” (page 2, lines 3–5). We have also used the suggested phrases on page 3, lines 13–15.*

- It is better to write: In Alagille syndrome fractures occur primarily in the lower limb long bones in the absence of significant trauma.

  *We have changed this sentence to “In Alagille syndrome, fractures primarily occur in the lower limb long bones in the absence of significant trauma.” (page 2, lines 7–9).*
Main manuscript

- pulmonary stenosis (pulmonary artery stenosis) (page 3, line 16-17).
- It may result from heterogeneous gene mutations. It is caused by mutations in the JAGGED1 gene in the overwhelming majority of cases, and by mutations in the NOTCH2 gene in 1-2% of cases.

We appreciate the reviewer’s comment. We have replaced this sentence with “Alagille syndrome is caused by mutations in the JAGGED1 gene in the overwhelming majority of cases, and by mutations in the NOTCH2 gene in 1–2% of cases.” (page 3, lines 17–18 to page 5, line 1).

- “Management of a pathologic lower extremity fracture in a child with Alagille syndrome is one of the most challenging problems in the orthopedic field.” This may be an overstatement, or exaggeration.

According to the reviewer’s comment, we have changed this sentence to “Management of a pathological lower extremity fracture in a child with Alagille syndrome can sometimes be a challenging problem in the orthopedic field.” (page 4, lines 9-11).

Case presentation

- On examination, she was found to be malnourished with stunted growth (height, 126 cm; weight, 19 kg). Centile value please

We have added centile values as suggested (page 5, lines 10–11).

Discussion

- Not as rare as this. Many cases are mild and it is underdiagnosed. 1 in 70,000 is usually quoted but this is considered an underestimate.

We agree with the reviewer’s comment. We have changed the following sentence: “Alagille syndrome is rare, occurring in 1 in 70,000 births, and affects both sexes equally [4].” (page 7, line 18 to page 8, line 1).

- The year of this report should be in brackets.

We have added the years of the reports for Lin et al (1997) (page 8, line 16) and Kapukaya et al (1998) (page 9, line 2).

- This paragraph is the 'Conclusion'

We have added the section “Conclusion” as suggested (page 11, line 11).

Discretionary:

- It would be good to know whether the diagnosis of Alagille syndrome has been confirmed by mutation analysis of the JAGGED1 gene - this is not stated. If the genetic test has not been performed this should be stated anyway.

According to the reviewer’s comment, we have added the following sentence: “A
genetic test was not performed in our case because the diagnosis of Alagille syndrome was already established based on the presence of distinct clinical features.” (page 5, lines 1–2).

Reviewer#2 (Dr Henry Dushan Edward Atkinson)

Major compulsory revisions

・ The English language needs tidying up by a Medical native English speaker. Aside from this, the case report is acceptable.

We have had our manuscript edited by a native English speaker with a medical background from a professional editing company.

・ There are a few fundamental mistakes and changes need to be made "It was considered difficult to do rigid fixation with an elastic nail because the femoral medullary cavity diameter was very small" Nailing is not a method by which one obtains rigid fixation. This should read "Elastic nailing was considered, however due to her narrow intramedullary canal this was judged to not be a viable fixation method". the same inaccuracy is then again repeated when you describe "rigidly fixing" the fracture with a frame. This is not rigid, and the fracture heals secondarily with callus!

We appreciate the reviewer’s comment on this important issue. We have changed the first sentence referred to by the reviewer to “Elastic nailing was considered; however because of her narrow intramedullary canal, this was judged to not be a viable fixation method.” (page 5, line 18 to page 6, lines 12). We have also replaced the second sentence referred to by the reviewer with “We decided to use a closed indirect reduction technique with an Ilizarov ring fixator and to decrease bleeding.” (page 7, lines 5–6).

・ the "conclusions" section should be termed "Discussion"

We have made this change as suggested (page 7, line 17).

・ There is nothing in the discussion about why the bone stimulator was necessary, nor any information about bony healing in Alagille syndrome. Surely the fracture would have healed just as quickly with the frame alone? "With the help of this treatment, the healing time and the duration of external fixation can be reliably shortened." - This statement cannot be justified, and there is no comparison, and again was the bone stimulator actually necessary? The discussion could have mentioned the normal healing times for femoral fractures in children, which are generally short.

We appreciate the reviewer’s comments. We have added the following sentences: “In Alagille syndrome, deficiency of intestinal bile acids ultimately interferes with the absorption of vitamin D, and failure of endochondral ossification is generally associated with the disturbance of absorption of vitamin D. However, the underlying mechanism
causing delayed union in Alagille syndrome remains unclear. Therefore, we consider that LIPUS might promote enhancement of endochondral ossification in femoral shaft fracture healing in Alagille syndrome.” (page 9, lines 14–18 to page 10, lines 1–2)