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PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Pediatrics

Manuscript NO: 61740

Title: Neonatal cholestasis can be the first symptom of McCune–Albright syndrome: A case report and review of literature

Reviewer's code: 03645097
Position: Peer Reviewer
Academic degree: MD
Professional title: Doctor
Reviewer's Country/Territory: United States
Author's Country/Territory: Japan

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Reviewer chosen by: Lian-Sheng Ma
Reviewer accepted review: 2020-12-22 17:50
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Review time: 2 Days and 7 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

In manuscript #61740, Satomura and colleagues present a case of a young boy with McCune-Albright syndrome (MAS) which was originally diagnosed as Alagille syndrome (ALGS). Due to the neonatal cholestasis, bile duct paucity in liver biopsy, peripheral pulmonary stenosis, renal phenotypes, and frequent fractures, the patient was thought to have ALGS. However, a causative mutation was not identified in JAG1 or NOTCH2, the two genes known to be mutated in ~ 96%-97% of ALGS patients. Later on, based on serum chemistry, and radiographic and bone scintigraphy analyses, the investigators suspected an MAS diagnosis. While no mutations in GNAS were identified in DNA extracted from patient's peripheral blood, a point mutation in this gene was identified in a bone biopsy (an later in the liver biopsy). The authors state that the identified mutation is an activating mutation, and conclude that the phenotypes can be explained by MAS. Finally, the authors provide a review of previous papers reporting hepatobiliary phenotypes in MAS patients and conclude that MAS should be considered in the differential diagnosis of patients presenting with neonatal cholestasis.

This is an interesting case and is likely to raise awareness in clinicians about the possibility of an MAS diagnosis in children with cholestasis, even when there is clinical and liver biopsy evidence supporting an ALGS diagnosis. The review of previous cases seems to be balanced, and the case is presented thoroughly. I have the following comments and suggestions for the authors:

Major points:

1. I don't know whether a diagnosis of ALGS can be excluded because of the identification of a GNAS mutation. It is theoretically possible for a patient to have both diseases. The reason I raise this issue is that the patient phenotypes suggestive of ALGS were not limited to the liver. Peripheral pulmonary stenosis is also a relatively common

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finding in ALGS patients. Moreover, a significant proportion of ALGS patients suffer from kidney disease as well. Furthermore, the bile duct paucity was very severe in this patient, although it could be that the biopsy was taken from the liver periphery and therefore was not representative of the status of the intrahepatic biliary system throughout the liver. I understand that the authors did not identify any mutations in JAG1 or NOTCH2. But a small percentage of patients with clinical criteria of ALGS do not have a mutation in any of these two genes. Due to these issues, the authors should consider keeping open the possibility that the patient has both diseases (or they can discuss in the manuscript how they think the pulmonary and kidney phenotypes might be explained by their mutation).

2. What is the basis for calling this mutation an activating mutation? Has it been identified in other patients and characterized to be activating? Without some experiments or reference to previous work, it is not clear whether this is indeed an activating mutation.

3. In the Discussion, the authors wrote "however, continuous stimulation of adenylyl cyclase has been suggested to play a role in bile metabolism". Bile duct paucity at that age is more likely to be caused by a failure to generate bile ducts as opposed to degeneration or injury. It is not clear how a role in bile metabolism can affect the number of bile ducts in the liver. The authors should remove this sentence and instead speculate how stimulation of adenylyl cyclase can potentially affect bile duct development. Alternatively, this paragraph can be removed.

Minor points:

1. Instead of "during liver biopsy", it's better to use "based on liver biopsy" or "in liver biopsy", because "during" would imply something happening while the biopsy is being performed on the patient.

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2. On page 4, lines 9-11, the authors wrote "Although mutation was not observed in the JAG1 gene by the fluorescence in situ hybridization analysis". This technique will presumably detect structural variations in JAG1 but not necessarily point mutations. Please clarify.

3. Same page, line 15: Instead of "His gene was further applied for a targeted next-generation sequencing", I suggest using "His DNA was further subjected to a targeted next-generation sequencing".

4. Please specify at what age the clinical assessment described under Physical examination section was performed.

5. In several places, the authors imply that PCR was used to identify the mutations. It's probably sequencing after the PCR. This should be clarified (unless I'm missing something).