Author's response to reviews

Title: Acute heroin intoxication in an infant chronically exposed to cocaine and heroin

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Author's response to reviews: see over
Dear Editor:

Through the electronic submission system of the Journal, we have uploaded the reviewed manuscript entitled "ACUTE HEROIN INTOXICATION IN AN INFANT CHRONICALLY EXPOSED TO COCAINE AND HEROINE", which is submitted to the consideration of the Editorial Board of JMCR for the section Case Reports. Neither the entire paper nor any part of its content has been published previously or is being submitted to another journal.

All authors have seen and approved the paper here uploaded.

We appreciate very much your attention to this submission.

Sincerely yours,

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Comments: (we have made all the changes suggested):

Reviewer 1

Discussion
1. The 2-nd paragraph should read: The mother's declaration regarding the possible ingestion of paracetamol-codeine by the infant, proved to be false....

Change has been made.
2. There should be no parenthesis after “codeine” at the end of the sentence.

   Change has been made.

3. In the next sentence, “ let hypothesize” should be changed to “suggests”.

   Change has been made.

4. Next sentence should read: The mother refused breast milk sampling, denied personal use of opiates….

   Change has been made.

5. In the next paragraph, “consequent” should be changed to “subsequent”.

   Change has been made.

6. 4-th paragraph should read: Since the baby was only one month old the high concentration of opiates and cocaine in his hair could not be attributed unequivocally to pre or post natal exposure to these drugs. These concentrations could be explained by either of these scenarios: permanent fetoplacental contact with a drug consuming mother during intrauterine life, passive inhalation or forced drug consumption, or by the infant putting contaminated objects in his mouth. In actual fact, the source and exact timing of exposure are of little consequence; the case report shows that, repeated exposure of an infant to cocaine and heroine was objectively highlighted by……..(10).

   Change has been made.

7. The last paragraph of the Discussion should be deleted, because there is a separate Conclusion subheading which is actually, a repeat of that last paragraph.

   Change has been made.

Table 1
8. The units for hair concentration should be placed next to the name of the drug in the top row.

   Change has been made.

Reviewer 2

1. The title is contradictory: Was it chronically or acute?

   The acute intoxication was for heroin and the chronic intoxication was for heroin and cocaine.
Following points have not been considered:

2. Urine of the infant should be tested for 6MAM as a definite heroin marker.

   This determination was not made in the previous laboratory and we had not any more urine sample.

3. The infant's blood/plasma concentrations of relevant drugs are missing.

   Blood was not sampled in the Emergency Room and no blood sample was stored.

4. The mother declared an acute codeine ingestion and morphine is a metabolite of codeine; the mother’s genotyping is missing (see the case of Koren et al. in Lancet).

   Yes, we reviewed this case in Lancet, but the mother genotyping is missing. The important thing was that 6-MAM comes only from heroin.

5. Drug concentrations in the infant’s hair could be the result of prenatal exposure;

   Sure, and it explains the chronic exposure as we say in the first paragraph of discussion.

6. The time window of exposure is not clear.

   It is difficult to say because neonatal hair doesn’t grow uniformly in all foetus during pregnancy.
   Probably, the infant’s hair corresponded to the last 2 trimesters of pregnancy plus the first month of postnatal life.

7. Quality of written English: Needs some language corrections before being published

   The new text has been reviewed by a native English speaker.

Reviewer 3

General Comments

1. The authors speak indistinctly about “acute poisoning” and “acute intoxication”. Homogeneity is required and I, personally, prefer “acute intoxication”.

   The change has been made.

2. When speaking about “drugs of abuse”, the authors sometimes refer to “drugs” and other times to “drugs of abuse”. If we considerer that the term
“drugs” is applicable to medical drugs, they must make precise in all cases that they are referring to “drugs of abuse”.

The change has been made.

Specific Comments
3. Title: the manuscript is entitled “Acute opioid intoxication in an infant ……”, taking into consideration the results of urinalysis, which show a ratio morphine/codeine in agreement with a heroin intoxication, the title would be better as “Acute heroin intoxication ………”.

The title has been modified.

4. Introduction: the authors refer to the advantage of hair for allowing a relatively long retrospective identification of substances. Nevertheless, a new paragraph explaining the long window of detection (from months to years) and the admitted growth rate (1cm/month according to the Society of Hair Testing) would be welcomed.

The change has been made.

5. Introduction: in the last paragraph it is not clear if, when speaking about the “rationale for this approach”, the authors are referring to the previous paragraph (Ref, 4,5) or to the aim of this manuscript. If they are referring to Ref. 4 and 5, a new paragraph with the objectives of this paper is required.

The change has been made.

6. Case report (page 3): the drugs of abuse tested in the screening by CEDIA must be specified.

The change has been made.

7. Case report (page 4): they only refer to unbleached maternal hair, but there is nothing about other types of cosmetic treatments.

The change has been made.

8. Discussion (page 4): Since, hair analysis demonstrated chronic exposure to heroin, specifically, in place of opioids, in general, the paragraph “….. in an infant chronically exposed to opioids and cocaine” should be changed to “….. in an infant chronically exposed to heroin and cocaine”

The change has been made.

9. Table 1: an additional column with the lengths of the hair samples from the father and the infant should be included. What do the two paragraphs included after the table (0-3 cm from the scalp and 0-12 cm from the scalp) mean?

Quality of written English: Needs some language corrections before being published
The change has been made. The manuscript has been checked over by a native English speaker.

**Required formatting changes:**

1. Authors contribution

XJ, analyzed the patient data, reviewed the literature and was a major contributor in writing the manuscript.
BF, analyzed the patient data and was a major contributor in writing the manuscript.
MS, was the clinician in charge of the child and contributed in writing the manuscript.
EC, was an important laboratory technician in biomarkers analyses and contributed in writing the manuscript.
RT, was the laboratory responsible and contributed in writing the manuscript.
AP, was the other clinician in charge of the child and contributed in writing the manuscript.
OV, was the paediatrician responsible for coordination of data and samples flow and contributed in writing the manuscript.
SP, was the major expert in laboratory analysis of biomarkers in alternative matrices and contributed in writing the manuscript.
OGA, analyzed patient data, reviewed the literature and the final manuscript, and was the main contributor in writing the manuscript.

All authors have seen and approved the final manuscript.

2. The manuscript has been checked over by a native English speaker.