Author's response to reviews

Title: Isolated enophthalmos: an uncommon gateway to orbital tumors in pediatrics. 9 month-old female presenting with isolated enophthalmos as the unique sign of a metastatic orbital tumor: a case report.

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Isolated enophthalmos: an uncommon gateway to orbital tumors in pediatrics.

9 month-old female presenting with isolated enophthalmos as the unique sign of a metastatic orbital tumor: a case report.

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Key words: Enophthalmos, Exophthalmos, Proptosis, Infantile orbital tumors, Neuroblastoma, Pediatric tumors.

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Dr Touhami: Drafting and revising the manuscript for content including medical writing for content, analysis and interpretation of data.
Dr Bui Quoc: Study concept, design, analysis and interpretation of data.

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Consent: Informed consent of the parents was obtained for the publication of this case report.
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Article type: Case report
Criterion: Unexpected or unusual presentations of a disease
Malignant orbital tumors are a rare and hazardous entity in both adult and pediatric populations. Histological origins are various and they are different in adults and children. Knowing the *prognosis of malignancy at such location* (near the central nervous system and important vascular features), clinicians are expected to prioritize their early diagnosis. Exophthalmos is the most commonly known symptom of such tumors especially in children where the neoplastic tissue tends to grow outwards given the narrowness of their bony structures. However, clinicians should not neglect that other signs can reveal these neoplasms and should remain cautious before the least symptom. As such, enophthalmos has already been described as a rare symptom of orbital tumors in adults in a few case reports. However it was generally the satellite of other preponderant accompanying signs that one usually cannot miss (mass, erythema, edema…) and more importantly it has never been reported as the unique indicator of an orbital neoplasm in pediatrics. The importance of early diagnosing these tumors is justified by their potentially disastrous prognosis and argues for the need of a perfect knowledge of their clinics, including the scarcest signs. Among these, enophthalmos is probably one of the least known. The case of this little girl alarmed us and made us choose to publish her story because the obvious lack of knowledge of this unusual association was brought to our attention at her expense. Her case deserves being reported because the diagnosis of her tumor was delayed by at least 3 months, which probably modified the prognosis, *because of a lack of knowledge of this unusual association.*

She in fact had been referred to 4 different paediatricians and pediatric
ophthalmologists at different teaching hospitals; however, all of them stated that her enophthalmos was nothing but a constitutional feature. The most important part of the story was that even the pediatric radiologists declined performing a CT scan because they believed that there was no valid justification for seeking an orbital tumor before enophthalmos alone. We report the case of a paediatric metastatic neuroblastoma revealed by enophthalmos alone and remind the importance of this sign as a revealing symptom of orbital tumors in children. The specificity of this case shows that enophthalmos can be the unique indicative sign of such hazard, which has not been clearly described elsewhere. The association between enophthalmos and orbital tumors is extremely rare in children and unfortunately not known in common practice of pediatrics. The authors believe it is extremely important to remind this statement to all practitioners because there can be no tolerance for ignoring this sign and delaying a potentially lethal diagnosis.
Revisions:
Reviewer 1

Subtitle: As suggested, “metastatic orbital tumor” was used instead of “malignant orbital tumor”

Abstract: As suggested, “metastatic stage 4” was changed for “stage 4 neuroblastoma”

Key words: The word "Neuroblastoma" was included

Case description:
1. We do agree that visual acuity is one of the most important clinical features. However, in pediatrics and especially in a 9 month-old child, such sign can only be approached by indirect signs including pupil size and reactivity to light, direct and consensual accommodation, fixation and following, binocular function, eye-hand coordination, reaction to patching and social behavior. All of these were found normal in the present case.
2. In the present case, the past medical history and birth history were perfectly unremarkable. The patient’s mother randomly discovered the enophthalmos of her child’s right eye approximately 3 months prior to presentation. She did not notice anything else but this backwards displacement of her child’s right eye, which urged her to consult various specialists.

Discussion
1. “Mammary carcinoma” was switched to “Breast cancer” as advised.
2. Possible mechanisms of enophthalmos in this case were suggested: First, structural modifications: by cracking the orbital wall, the tumor probably modified the eyeball position dragging it downwards and backwards. Second,
the eyeball was probably dragged backwards as a consequence to a retractile phenomenon consecutive to muscle and/or fat tissue infiltration by the neuroblastoma. Third, but this is probably less likely, the growth of the neuroblastoma could have induced a shrinking of the orbit’s other components including fat, causing a backwards displacement of the eye.

**The other causes of osteolytic diseases** were voluntarily not detailed in this case report because the focus was not on such causes. The purpose of this work was to put light on a very poorly known feature: enophthalmos, as a revealing sign of orbital tumors.

**Photos:** Informed consent was obtained from the parents to publish this case with all the necessary material including CT scans, lab results etc. However, given the seriousness of their child’s disease, they denied the use of a photograph in which the latter could be recognized, which one could perfectly understand given the circumstances. It is worth knowing that clinically speaking, this child’s enophthalmos was so mild that four consecutive specialists failed recognizing it, stressing the importance of having in mind this symptom. We do agree that nothing replaces the strength of a photograph, however the message supported herein is still worth being published because it remains a very unusual presentation. CT scans presented in this case are still very suggestive and clearly show the right enophthalmos and the malignant mass. This article is valuable in showing a very rare symptom of enophthalmos in a child with malignant orbital disease.
Reviewer 2

1. We do perfectly agree that the paper lacked proof of enophthalmos in this case. As explained earlier, the parents denied the use of a photograph for personal reasons given the seriousness of their child’s disease. CT scans showed the enophthalmos of the right eye on various cross-sections with an oculo orbital index < 30%. Figure 1a clearly shows the enophthalmos of the right eye comparatively to the left eye.

2. As explained in the reviewer 1 section, causes of enophthalmos in this case were suggested in the discussion section.

    Imaging evidence evoking enophthalmos was added in figure 1a.

3. In page 4, 2nd paragraph, the authors said that “In fact, enophthalmos is a posterior displacement of the eyeball within the orbit but its diagnosis remains tricky because there is no agreement on a clear definition.” This statement was to stress the difficulty of diagnosing enophthalmos clinically. In fact, one could always use an exophthalmometer, however, there is not any clear exophthalmometric consensus defining enophthalmos in the literature, especially in pediatrics.

All modifications were included in the manuscript file as suggested.