Author's response to reviews

Title: A postoperative neurological aggravation with sevoflurane in patient with Xeroderma Pigmentosum: a case report.

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Author's response to reviews: see over
Cover letter

I am really thankful for your appealing comments and I would like also to converge toward the different remarks that you have mentioned. We tried to take them into account in the revised manuscript.

You will find in this document, reviewers comments that are written in red, our answers are written in black

Responses to comments

Reviewer: Irene Asouhidou

1. Minor: Sharp reflexes and Babinski reflex were ‘positif’. Change to “positive”.
   Changes are made

2. Authors did not explain the delay of extubation (4 hours after arriving in the recovery room)
   Anesthetic management in the recovery room as described in the revised manuscript:

In the postoperative recovery room, the patient remained intubated and ventilated. The absence of unexplained awakening after about 1 hour induced us to put into practice a monitoring of curarization with neostigmine administration. The motor response was satisfactory. However, not waking up and not return to spontaneous ventilation after 2 hours induced the creation of a biological assessment that shows no abnormalities (sodium, urea, glucose). In three postoperative hour, we noticed a return of signs of awaking and spontaneous breathing. Tidal volume was satisfactory, and patient developed agitation, abnormal movements which persisted despite the extubation, optimization of analgesia and a
psychological abort. At examination, signs of pyramidal irritation appeared, which necessitates transferring the patient to MRI’s room, whose images did not show any lesion that could explain these symptoms.

**Reviewer: Peter Merjavy**

There is some uncertainty wheather MRI was performed before and after the surgery, or only after the operation?

The patient has been followed up for XP; a preoperative MRI was performed after the installation of neurological signs in a sort of ataxia and extremities tremor. The second MRI was performed on after deterioration of the cognitive functions in the postoperative period.

Have you considered other regional anesthesia techniques for fractured neck of femur (lumbar plexus block or 3in1block in combination with parasacral block)? If not, why?

Unfortunately, the other regional anesthesia techniques were not contemplated due to the time required for their implementation, and the surgical team was ready for intervention. On the other hand, the neurological status of the patient was not worrying and there was no contraindication for general anesthesia’s agents in that kind of patients. So, the choice of general anesthesia seems to be safe.

Several authors recommended use of TIVA for XP patients. Was TIVA unavailable at that time in your hospital or is there any other reason why you haven’t considered total i.v. anesthesia for your patient?

The total intravenous anesthesia was available at time of operation, but our choice was for sevoflurane because it is used in our hospital since 2006 with approximatively 30 operations per day. Its safety is demonstrated and there was no similar complication although our directory remains poor for patients with XP.
You have used muscle relaxant (cisatracurium), so I presume that you have intubated this patient. Have you considered use of LMA for general anesthesia as patients with XP are sensitive to muscle relaxants?

In everyday practice, the surgical team of traumatologists is always used to operate this kind of patient in the lateral position with an average duration which exceeds 60 minutes, and which is not appropriate for the use of LMA. Thus, because of preserved muscle strength of our patient, the use of muscle relaxants appears to be warranted with a single dose associated to body weight (0,15mg/Kg).

Reviewer: Alain SARASIN

The description is interesting since most of XP patients have to go often to surgery due to their high numbers of tumours.

I have two types of comments. One on the genetics of XP and others on the anesthesia. A major point missing in this paper is the type of XP of the described patients. Indeed there are 7 different genes involved in classical XP (XPA to XPG) and one gene for XP variant. It is important to know which type of gene is involved in the patient because only XPC, XPE and XP variant patients don't have neurological disorders while the others show major and progressive neurological abnormalities as indicated in the discussion of the paper and reference 8. The majority of XP patients in Morocco belong to the XPC group with no neurological abnormalities, but also a large numbers of patients are XPA and XPD, which are characterized by a progressive neurological deterioration. The authors, if they don't know the gene involved, should at least better described the clinical features of their patient, particularly they should tell us what is the neurological state of the patient before the surgery. The implication of their discovery is,
of course, very different if the patient did not exhibit any neurological abnormalities before the surgery, or if she did.

The datum-points that we have had during the examination of the patient and his family were not in the position to know the type of XP. What we have known is that this patient has been followed up since her early childhood, for a disease in the form of cutaneous minor; she had never a tumor surgery. She had a slight decline in IQ (intelligence quotient), and an end tremor of the extremities with a running ataxic. In the preoperative examination, patient was calm cooperating and oriented in time and space, with preserved muscle strength and deep tendon reflexes without anomalies. A preoperative MRI did not show any signal of brain’s abnormalities.

The authors did not tell us if this abnormal reaction to sevoflurane was observed in their clinical practice with non-XP patients. If this abnormal response was not described previously with their other patients they should tell us approximately how many patients have been through anesthesia using the same protocol.

The experience of our anesthesia department with the use of sevoflurane started in 2006 with approximately 30 surgeries per day. We confirm that there is a secure and malleable use of this halogenated with no similar complication to this case report.

Before incriminating the sevoflurane, you have to eliminate the other causes as post-operative O2 desaturation, residual paralysis or seizures:

-Did you monitor the BIS during surgery and did you think that this monitoring would improve the adjustment of anesthesia depth?

The monitoring of BIS would be very helpful in the adjustment of anesthesia depth. But during the general anesthesia, the neurological state of this patient was not worrying as the surgery was with an average duration. So, in our view, it was unnecessary to monitor the BIS.
Did you monitor the level of muscle paralysis after cisatracurium injection? We know that XP patients are sensitive to muscle relaxants due to the neuronal dysfunction. This point must be discussed.

The XP patients are generally sensitive to muscle relaxants. But in our case muscle strength was preserved, and it was necessary to intubate the patient, then we used non-depolarizing curares with a single dose: 0.15 mg / kg of Cisatracurium.

The monitoring of curarization has been done in the recovery room where a decurarization by neostigmine was performed after TOF response value at 0.9 about 1 hour after admission to the room.

You have to describe the recovery of the anesthesia: Delay of recovery after end of surgery, reversal of muscle relaxant, ventilator weaning etc. What happens during the 4 hours before awaking in the recovery room?

In the postoperative recovery room, the patient remained intubated and ventilated. The absence of unexplained awakening after about 1 hour induced us to put into practice a monitoring of curarization with neostigmine administration around 1H. The motor response was satisfactory. However, not waking up and not return to spontaneous ventilation after 2 hours induced the creation of a biological assessment that shows no abnormalities (sodium, urea, glucose). In three postoperative hour, we noticed a return of signs of awaking and spontaneous breathing. Tidal volume was satisfactory, and patient developed agitation, abnormal movements which persisted despite the extubation, optimization of analgesia and a psychological abort. At examination, signs of pyramidal irritation appeared, which necessitates transferring the patient to MRI’s room, whose images did not show any lesion that could explain these symptoms.

- Did you record SpO2 after surgery and how long she stayed in recovery room?
In the recovery room, the monitoring of SpO2 was continuously throughout the intervention, and we did not notice any decrease of its value. The patient remained in the recovery room for 4 hours where etiological exploration for unexplained delay of awakening and appearance of abnormal neurological signs like persistent agitation, confusion and pyramidal irritation. The last exploration was a postoperative MRI which showed no abnormal lesions.

4) There is lack of evidence to suggest volatile anesthetics-induced neurotoxicity in humans. In this regard, the contribution of general anesthesia/anesthetics to postoperative cognitive decline has not been established. This point should be discussed. There are recent papers recently published by Zuo Z. on this subject. Because, XP patients are often anesthetized, it is important to answer these questions before incriminating this type of anesthetic, which is regularly used.

In the revised manuscript, we mentioned in details that the contribution of the general anesthesia/anesthetics in the POCD is not well established and factors unrelated to anesthesia could occur in this clinical entity.

**Reviewer: William Donaldson**

The case is interesting. The condition is rare, but the authors make a case for Considering TIVA whenever it is encountered.

However, there is no hard evidence given that sevoflurane caused the issue - this is merely speculated upon by reference to similar cases some of which were in vitro experiments, and while the authors do address this I feel that more emphasis should be made of this fact.

We suggested to TIVA in diseases of XP neurological signs without any against states of the use of sevoflurane. The current data do not have concrete evidence of halogenated induced
neurotoxicity in XP patients. Our attitude was based on practical experience of this patient and the other reported cases.

There are some language errors (grammatical and spelling) which will require correction.

Remark taken into account in the revised manuscript.

**Reviewer: PJ Brooks**

In my view, it is difficult to draw any firm conclusions from this report. While some XP patients do in fact have a neurodegenerative disease phenotype, it is not clear to me that this patient is one of them. Also there is no information about the mutations or the patients complementation group that would be useful to have. Finally, the patient was given many different drugs; it's hard to point specifically to one as being a potential cause.

As we described in the revised case report, it always difficult may be impossible to separate the effect of each drug on the brain XP patient. But, in our case, there was any surgical factor or event during anesthesia could explain the irreversible neurological decline. Volatile anesthetic still be the most anesthetic agents involved in the toxicity of brain at experimental level. We are not sure it will be the cause, but we would like to discuss its genotoxic bad effect and to review XP cases anesthetized with sevoflurane. Our final is to suggest authors more searching about sevoflurane induced neurotoxicity and genetic disorders in XP patients.