Reviewer’s report

Title: A retrospective analysis of adrenal crisis in steroid-dependent patients: causes, frequency and outcomes

Version: 0 Date: 05 Jun 2019

Reviewer: Laurence Guignat

Reviewer's report:

The author of the present article conducted two online surveys in 2013 and in 2017-18 of adrenal insufficiency's patients, mostly members of UK support groups, asking about patients' experiences of adrenal crisis (AC), with huge number of responses (1054 or 1053 for the 2013 survey [1054 in the text versus 1053 in the table] and 746 for the 2017-18 survey). The originality of this article is to have the patients' point of view in real life.

Several major comments:
1. The number of responses to questions in charts are significantly lower than the number of patients that experienced at least one AC (535 to 536 [data forgotten in chart 2] versus 1053 or 1054 respondents x 63% that experienced 1 or more AC = about 700 for 2013 survey; 467 to 480 versus 746 respondents x 67% that experienced 1 or more AC = about 500 for 2017-18 survey). The number of analyzable questionnaires should be better clarified.
2. Incidence of AC varies depending on the cohorts (self-reported episodes with patients from Endocrinology department or members of support group / hospital records / insurance records…), as mentioned by the author. Patients who have already had a crisis and have identified it as an adrenal crisis (and not as a gastroenteritis) are probably more willing to answer a questionnaire on this topic, but these patients are also most at risk for another crisis, as demonstrated in the only prospective study to date (Hahner et al JCEM 2015). Incidence of AC varies also on the various definitions of AC. Every adrenal emergency that need to adapt treatment cannot be considered as an AC. If all the events that need to adjust the hydrocortisone dose (orally or parenterally) are take into account, the frequency is necessarily higher than those of the crises defined by needing injected hydrocortisone. According to the definition used for the present surveys (injected steroids and/or intraveinous fluids), adrenal events managed only with oral hydrocortisone should not have been take into account. However, these patients represent 6.5 % in 2017-18 and 6.2 % in 2013 in the chart 3. Furthermore, the author suggests that low daily doses may explain the high frequency, but an association between lower doses of glucocorticoid and AC risk, has never been demonstrated (Hahner et al JCEM 2015, Rousseau et al Plos One 2015, Notter et al Swiss Med Wkly).
3. It should be more clearly stated in the abstract that there were 2 surveys (2013 and 2017-18). Results should be presented in a more structured (frequency of AC, risky situations, location, management of hydrocortisone injection, hospitalization, time to treat, satisfaction) and detailed way (other risky situations apart from vomiting; time to treat: time between arrival and glucocorticoid injection? (and when hydrocortisone injection is already done by patients / relatives, how to judge if it is necessary and when?) time between arrival and IV fluids? time between arrival and the treatment of
the triggered factor ?).
4. Discussion elements are wrongly included in the results (education materials, registration with ambulances). The results of these surveys should be compared to those of 2003 and 2006 published by the same author (and Wiebke Arlt) previously (European Journal of Endocrinology 2010).
5. There is no statistical analysis (while percentages are compared like proportions of self-injection and of injection from an ambulance crew, satisfaction levels and time to treat,…).
6. Many references do not correspond to scientific articles but to education / information materials (ref 18, 19, 20, 21, 22, …) (it is interesting to know them but it may be necessary to present them otherwise) or to abstracts (ref 5, 7, 14) while major references are missing (especially for epidemiology of adrenal insufficiency, epidemiology and mortality due to AC).
7. This study has other limitations than the one stressed by the author: it is a retrospective analysis in patients suffering from adrenal insufficiency for many years thus it might be difficult to remember, for a rare event, even the most recent one in details.

Other comments:
1. Self-injection by patients and relatives should be done subcutaneously (and not by IM as suggested by the author p.5)
2. p8 : Vomiting and diarrhea are not synonymous of infective gastro-enteritis. As indicating mater by the author, gastrointestinal signs might be signs of AC triggered by factors such as viral infection.
3. p8 : The way the question is phrased ("what factors have seemed to be a cause fo the various adrenal emergencies....") does not allow to specify whether the factors were isolated or associated.
4. p 14-15, in discussion, one should question the obstacles to the realization of the injection by the patient or relatives.
5. The following sentence (abstract p4) is not clear: "More did so than received their initial parenteral hydrocortisone from any other source…"

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

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