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Column: Review

Title: New insights into the pathophysiology of achalasia and implications for future treatment

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Reviewer code: 03548284, 03026706 and 03476277

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Scientific editor: Jing Yu

Dear Editor and Referees,

Thank you for your comments concerning our manuscript. These observations are all valuable and very helpful for revising and improving our paper, as well as an important guiding significance to our researches. We have review the comments carefully and made the corrections.

Reviewer 1

In the manuscript, the authors have reviewed the recent findings on etiology and pathophysiology of the idiopathic achalasia. The literature review is detailed accurate and comprehensive, and the contents are valuable to the readers. However, the contribution of those advances to the treatment strategy of achalasia is not very obvious. And in the article, the authors only describe the possible causes such as ganglion cell loss, infections, autoimmunity, inflammation, autoantibodies and genetics, respectively. I want to know what are the possible common points or key connections among those factors, which may bring hope for cure the disease in the future.

- As suggested by the reviewer a summary table of all the pathophysiology and the potential therapeutic targets was included in the manuscript (Table 2) where key connection considers inflammation and fibrosis.

Reviewer 2

The authors performed a revision regarding the new insights into the pathophysiology of achalasia and implications for future treatment. The most important theories are reviewed and treatment options are well described. Despite being an interesting review article some aspects could be imporved:

1. A table that summaries all the pathophysiology theories should be provided by the authors

- As suggested by the reviewer a summary table of all the pathophysiology was included in the manuscript (Table 2).

2. The actual treatment algorithm for achalasia should be described in the article.

- As suggested by the reviewer a actual treatment algorithm was included in the manuscript (Figure 6).

3. The authors should be provide a table with the most important treatment options.

- As suggested by the reviewer a summary table with the most important treatment options was included in the manuscript (Table 1).

4. The authors should mention the use of esophageal self-expanding metal stent (SEMS) for Achalasia treatment.

As suggested by the reviewer a the next paragraph was included in the manuscript: Another treatment alternative for the treatment of achalasia includes self-expanded metal stents (SEMS). Experience is limited using this treatment option and includes a study with 75 achalasia patients in which a 30 mm SEMS was temporally placed under fluoroscopic guidance. After 4-5 days, SEMS where endoscopically removed and patients followed for up to 10 years. Success rate at 1 month was 100% and 83% at 10 years (Zhao JG, Li YD, Cheng YS, et al. Long-term safety and outcome of a temporary self-expanding metallic stent for achalasia: a prospective study with a 13-year single-center experience. Eur Radiol. 2009;19(8): 1973–1980.). Another study compared the efficacy of different SEMS diameters (20, 25 and 30 mm) in achalasia patients. A total of 90 patients were included and followed at 10 years and showed better success rate (83.3%) with a 30 mm SEMS compared to lower diameters (Li YD, Cheng YS, Li MH, Chen NW, Chen WX, Zhao JG. Temporary

self-expanding metallic stents and pneumatic dilation for the treatment of achalasia: a prospective study with a long-term follow-up. Dis Esophagus. 2010;23(5):361–367.). SEMS have shown promising results but experience is limited to a single institution and cannot be widely recommended and more studies are needed in order to include this in the treatment algorithm for the treatment of achalasia.

Reviewer 3

Congratulations on your text. The review is very complete, and the subject is very well chosen, as achalasia affects many people and, as you wrote, its pathophysiological mechanism is yet uncertain.

We authors appreciate the careful and thoughtful reading of our manuscript.