Peer Review File

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Reviewer A

The authors present a literature review of styloidogenic jugular vein compression. They have included manuscripts identified in a pubmed search, and combined the patient biological data, radiological data, treatment data, and outcome data. They conclude that styloidogenic compression of the jugular vein may be an important disease that may be able to be treated perhaps best with a combined endovascular and open surgical approach.

There are several concerns with the fundamental concept of this manuscript, with lack of following and presenting standard data, as well as an oversight of data available regarding potential complications.

Comment 1: It is not clear that styloidogenic compression of the jugular veins is pathologic. There are not studies to compare symptomatic patients against controls. In addition, the symptoms presented are quite vague, and rely on patients to report symptom improvement. This obviously leaves considerable room for the effects of placebo. In addition, this exact radiological finding has been previously proven to not be pathologic, but only after hundreds and hundreds of MS patients were treated. Let's not make the same mistake again. This is not discussed.

Reply 1: We agree with the reviewer: nowadays there is still not enough evidence clearly demonstrating styloidogenic compression of the jugular veins is pathologic. Clinically relevant extrinsic compression on the extracranial internal jugular vein due to an elongated styloid process has been rarely described in literature. A study by Jayaraman et al. {{443 Jayaraman 2012;}} enrolled 108 patients whose CT angios were investigated for the incidence of internal jugular vein compression by extrinsic structures in the upper neck. They found 24.1% right side compressions and 30.6% left side compressions. They concluded that jugular vein compression is an anatomic variant and unlikely to be pathologic in nature. However, they did not investigate the reasons why these CT angios were performed or patients' clinical history, so it can be considered only a radiological report with a total lack of clinical correlation.
The rationale to hypothesize a possible pathological potential of styloidogenic jugular compression lies in the following considerations.
In the Gadda-Ursino hemodynamic model for the study of cerebral venous outflow, a jugular stenosis may have a strong effect on venous sinuses pressure, which reaches values as high as 13–16 mmHg both in supine and upright positions.{{625 Gadda,G. 2015;}} These findings have been already clinically confirmed by Esfahani who used quantitative magnetic resonance

venography (qMRV) to measure the venous sinus flow in patients undergoing endovascular stenting and identified a relationship with intravenous pressures.{{630 Esfahani,D.R. 2015;}} The analysis of the change in intravenous pressure and qMRV flow showed a linear relationship (Pearson correlation r = 0.926). The venous pressure is strongly correlated to cerebro-spinal fluid (CSF) dynamics. {{616 DE Simone,R. 2017;}} A computational study quantified the effect of internal-jugular vein function on intracranial venous haemodynamics, with particular attention paid to venous reflux and intracranial venous hypertension. This study concluded that the clinical implications of the findings are unknown, though they may relate to recent hypotheses linking some neurological conditions to extra-cranial venous anomalies.{{855 Toro,E.F. 2015;}}
A venous flow impairment, even monolateral, due to the styloidogenic compression could bring an imbalance in this sensitive venous-CSF mechanism, resulting in causing symptoms (hedache, tinnitus, insomnia, visual impairment ecc) not unexplainable otherwise with neurosurgical/ENT pathologies.

We agree with the reviewer that symptoms described and reported in literature are often aspecific and generic. This is the reason why we decided to make this review trying to collect and classify main symptoms and signs. Indeed, we found headache, tinnitus and insomnia are the most common ones (see results section).

Recently, a systematic review identified moderate-quality evidence that, compared with sham procedure, venous PTA intervention did not provide benefit on patient-centred outcomes (disability, physical or cognitive functions, relapses, quality of life) in people with MS. {{829 Jagannath,V.A. 2019;}}However, the vein stenosis associated to chronic cerebrospinal venous insufficiency (CCSVI) and MS usually consists of an anomalous extracranial venous outflow related to multiple significant extracranial venous stenosis, localized at the cervical, thoracic and, less commonly, abdominal level of the principal cerebrospinal venous segments. {{768 Zamboni,P. 2009;}}
Styloidogenic jugular compression is a very specific type of jugular stenosis, mainly involving J3 stenosis and has not been associated with MS. Indeed, we do agree with the reviewer that surgical or endovascular treatments should be considered after failure of conservative treatment and need to be carefully evaluated and validated with stronger evidence (RCTs?) in order to really understand beneficial effects and possible complications. Our results only suggest these kinds of treatment could have a role in the treatment of styloidogenic jugular compression.

Changes in the text:
Discussion, page 8: Clinically relevant extrinsic compression on the extracranial internal jugular vein due to an elongated styloid process has been rarely described in literature. A study by Jayaraman et al. {{443 Jayaraman 2012;}} enrolled 108 patients whose CT angios were investigated for the incidence of internal jugular vein compression by extrinsic structures in the upper neck. They concluded that jugular vein compression is an anatomic variant and unlikely to be pathologic in nature. However, they did not investigate the reasons why these CT angios were performed or patients' clinical history, so it can be considered only a radiological report with a lack of clinical correlation.

Discussion, page 9: The rationale to hypothesize a possible pathological potential of styloidogenic jugular compression lies in the following considerations.
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Discussion, page 11: The surgical or endovascular treatments should be considered after failure of conservative treatment and need to be carefully evaluated and validated with stronger evidence (RCTs?) in order to really understand beneficial effects and possible complications. Our results only suggest these kinds of treatment could have a role in the treatment of styloidogenic jugular compression.

Comment 2: The authors should not include case reports, or case series that are very few in numbers. The authors should present the flow chart of the data acquisition. A table of the summary of the included manuscripts should also be presented.

Reply 2: we thank you the reviewer for the suggestions. We created the flow chart of the data acquisition and Table 5, collecting authors, year of publication, study type and number of patients of all studies included in the review. We agree with the reviewer case reports or case series should be avoided but unfortunately, since the styloidogenic compression of jugular vein is a new nosological entity and few reports are available in literature, only 2 studies included more than 20 patients (see table 5). For this reason, we decided to also include case reports and case series.
Changes in the text: we added figure 2 and Table 5.

Comment 3: The authors obliquely mention jugular venous stenting for treatment of multiple sclerosis. This has been clearly shown to not be a legitimate cause or treatment for MS, but the complications are well known and documented. The comparison here is obvious and should be

mentioned by the authors. The reported and potential complications of stenting (migration, stent fracture when squeezed between two bony structures) should be discussed as well.

Reply 3: we agree with the reviewer. Although the styloidogenic jugular compression and the MS are 2 different and separated nosological entities, and in most of the included papers complications are rarely reported and discussed, we should mention them. For this reason, we added a paragraph about potential complications of endovascular and surgical treatments.

Changes in the text:

Page 11-12**.** Although complications are rarely reported and discussed in the included papers, these must never be underestimated. Endovascular venous stenting has been associated to stent migration or fracture, pseudoaneurysms formation, jugular vein stent thrombosis, cerebral sino-venous thrombosis, cranial nerve injury and injury associated with venous catheterization. {{830 Burton,J.M. 2011;}}

Surgical complications are represented by wound infection, postoperative hematoma, facial weakness, dysphasia, accessory nerve or facial nerve injury. {{477 Higgins 2017;}}

While some complications can be asymptomatic (like vein thrombosis and stent migration), these patients face future risks including the potential need for long-term anticoagulation and the possibility of stent thrombosis. When performing this kind of procedures, physicians should be mindful of potential risks, and continue to develop strategies to monitor and manage these patients.

Comment 4: The lack of manometry data is very concerning. How could unilateral stenosis cause venous hypertension (the presumed pathophysiology mechanism)? The venous system is a parallel flow circuit. Opening one limb of the circuit decompresses the entire system. The inclusion of manuscripts that do not include manometry renders the final results doubtful.

Reply 4: We agree with the reviewer the lack of manometry data is very concerning, since they were reported in only 28 cases. We added this consideration in the limits paragraph. Unfortunately, due to the limited number of literature reports about styloidogenic jugular compression, we decided to include also case series not reporting manometry.

The rationale to hypothesize a possible pathological potential of styloidogenic jugular compression lies also in the following considerations.

In the Gadda-Ursino hemodynamic model for the study of cerebral venous outflow, a jugular stenosis may have a strong effect on venous sinuses pressure, which reaches values as high as 13–16 mmHg both in supine and upright positions.{{625 Gadda,G. 2015;}} These findings have been already clinically confirmed by Esfahani who used quantitative magnetic resonance venography (qMRV) to measure the venous sinus flow in patients undergoing endovascular stenting and identified a relationship with intravenous pressures.{{630 Esfahani,D.R. 2015;}} The analysis of the change in intravenous pressure and qMRV flow showed a linear relationship (Pearson correlation r = 0.926). The venous pressure is strongly correlated to cerebro-spinal fluid (CSF) dynamics. {{616 DE Simone,R. 2017;}} A computational study quantified the

effect of internal-jugular vein function on intracranial venous haemodynamics, with particular attention paid to venous reflux and intracranial venous hypertension. This study concluded that the clinical implications of the findings are unknown, though they may relate to recent hypotheses linking some neurological conditions to extra-cranial venous anomalies.{{855 Toro,E.F. 2015;}} A venous flow impairment, even monolateral, due to the styloidogenic compression could bring an imbalance in this sensitive venous-CSF mechanism, resulting in causing symptoms (hedache, tinnitus, insomnia, visual impairment ecc) not unexplainable otherwise with neurosurgical/ENT pathologies.

In addition, we agree with the reviewer that the venous system itself can be considered as a pure mechanical parallel system. However, the relationship and the balance with the CSF dynamics is a more complex system. In 2012 a group of researchers hypothesized the existence of the "glymphatic system". According to them, subarachnoid CSF enters the brain rapidly, along the paravascular spaces surrounding the penetrating arteries, then exchanges with the surrounding interstitial fluid. Similarly, interstitial fluid is cleared from the brain parenchyma via the paravascular spaces surrounding large draining veins.{{831 Iliff,J.J. 2012;}}

Impairment in venous drainage reflects on CSF dynamics that could be responsible of several symptoms associated to styloidogenic jugular vein compression (headache, tinnitus, visual disturbances). {{833 Guo,P. 2019; 832 Grech,O. 2020; 834 Atsumi,H. 2020;}}

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Discussion, page 9: The rationale to hypothesize a possible pathological potential of styloidogenic jugular compression lies in the following considerations.

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Reviewer B

Comment 1: Could the authors provide more details on statistical methods use to pool data from these 14 selected studies? Did the authors manage to obtain individual data from each selected study? Is this an indidividual patient data meta-analysis?

Reply 1: unfortunately, statistics was not applied, because of the heterogeneity of the data. Indeed, we tried to obtain individual data from each selected study, however in several studies this was not possible, and we collected only overall data of patients. This constitutes a limit and we provided in specifying it in the text.
Changes in the text:
Limits, page 13. Unfortunately, statistics was not applied, because of the heterogeneity of the data. Indeed, we tried to obtain individual data from each selected study, however in several studies this was not possible, and we collected only overall data of patients

Comment 2: No data is presented concerning definition of an elongated styloid process or a narrowed C1-styloid process distance or IJV compression (reduced cross sectional area versus minimum diameter of IJV ?). Based on the 14 selected articles, could the authors provide more information regarding these definitions?

Reply 2: we agree with the reviewer. One of the major issues of styloidogenic jugular compression is the lack of a standardized definition. We carefully analyzed definitions and methodologies reported in the 13 papers we included in the review. Indeed, most of the papers are case reports and refer generally to “elongated styloid process” or “jugular stenosis” or “compression from the transverse process of C1 combined with the styloid process”. Only the study by Ding et al. {{811 Ding,J.Y. 2020;}} described in the methods section the definition of jugular stenosis as: “Patients with cervical spondylotic IJVS should comply with each item as follows: (a) the stenotic segment narrowing of ≥50% in respect to the proximal adjacent jugular vein segment, as shown in MRV, CTV, or CV; (b) at least one abnormal collateral vessel ≥50% of the maximal diameter of the adjacent IJV or at least two abnormal collateral vessels <50% of the maximal diameter of the adjacent IJV, as depicted by MRV, CTV, or CV; (c) IJVS secondary to the compression from the cervical lateral mass with or without the styloid process, as depicted by CTV; (d) with unexplained non-focal neurological deficits or other symptoms.”;

and the study by Bai et al.{{796 Bai,C. 2020;}} : “IJVS patients with eagle syndrome should meet the following criteria: (I) The stenotic IJV segment of the unilateral or bilateral IJV was more than 50% compared to the proximal adjacent IJV segment, which can be visualized at contrast-enhanced magnetic resonance venography (CE-MRV), computed tomographic venography (CTV) or catheter venography (CV). (II) Abnormally distorted collateral vessels were confirmed by CE-MRV, CTV or CV. (III) Patients presented with nonspecific clinical symptoms: headache, tinnitus, head noises, visual disorders, hearing loss, memory loss, insomnia, anxiety and neck discomfort. (IV) IJVS secondary to elongated styloid process compression was confirmed by CTV and 3D reconstruction of CT scanning.

Nevertheless, for future studies on this topic we should advice the use of a clear definition of jugular stenosis such as a reduction of vessel caliber >80%, based on diameter reduction on axial cuts compared with diameter of normal vein proximal to the stenosis (according to Jayaraman criteria {{443 Jayaraman 2012;}}) and the use of criteria described in Ding et al. and Bai et al. papers.{{811 Ding,J.Y. 2020; 796 Bai,C. 2020;}}

We included this consideration in the “Open issues and future perspective” paragraph.

Changes in the text:

Page 12, Open issues and future perspective: One of the major issues of styloidogenic jugular compression is the lack of a standardized definition. We carefully analyzed definitions and methodologies reported in the 13 papers we included in the review. Indeed, most of the papers are case reports and refer generally to “elongated styloid process” or “jugular stenosis” or “compression from the transverse process of C1 combined with the styloid process”. Only 2 papers by Ding et al. and Bai et al. reported cleared and defined criteria to define styloidogenic jugular compression.{{811 Ding,J.Y. 2020; 796 Bai,C. 2020;}} Nevertheless, for future studies on this topic we should advice the use of a clear definition of jugular stenosis such as a reduction of vessel caliber >80%, based on diameter reduction on axial cuts compared with diameter of normal vein proximal to the stenosis (according to Jayaraman criteria {{443 Jayaraman 2012;}}) or the use of criteria described by Ding and Bai.{{811 Ding,J.Y. 2020; 796 Bai,C. 2020;}}