A novel intraoperative ultrasound probe for transsphenoidal surgery: first-in-human study

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Abstract

Background: Ultrasound has been explored as an alternative, less bulky, less time-consuming and less expensive means of intraoperative imaging in pituitary surgery. However, its use has been limited by the size of its probes relative to the transsphenoidal corridor. We developed a novel prototype that is more slender than previously reported forward-viewing probes and, in this report, we assess its feasibility and safety in an initial patient cohort.

Method: The probe was integrated into the transsphenoidal approach in patients with pituitary adenoma, following a single-centre prospective proof of concept study design, as defined by the IDEAL guidelines for assessing innovation in surgery (IDEAL stage 1 – Idea phase).

Results: The probe was employed in 5 cases and its ability to be used alongside the standard surgical equipment was demonstrated in each case. No adverse events were encountered. The average surgical time was 20 minutes longer than that of 30 contemporaneous cases operated without intraoperative ultrasound.

Conclusion: We demonstrate the safety and feasibility of our novel ultrasound probe during transsphenoidal procedures to the pituitary fossa, and, as a next step, plan to integrate the device into a surgical navigation system (IDEAL Stage 2a – Development phase).

Background

Pituitary tumours are common, affecting 15-20% of the population[1] and the transsphenoidal approach is the preferred corridor to access these lesions when surgery is indicated. However, despite advances in microsurgical and endoscopic technique,[2] some pituitary tumours remain difficult to cure. About a third of patients undergoing transsphenoidal surgery will have an incomplete resection.[3] As a consequence, different intraoperative imaging modalities have been explored to address this shortcoming, including magnetic resonance imaging (MRI) and computed tomography (CT).[4, 5] Although both intraoperative MRI and CT can provide high-resolution images, their bulkiness, cost and impact on the duration of surgery related to the acquisition of images, can all be advanced as obstacles to their regular and widespread use, not only in transsphenoidal surgeries but in neurosurgical procedures in general.

Intraoperative ultrasound presents with several advantages in this regard and so, has been investigated during intracranial procedures as an alternative means of intraoperative imaging for real-time intraprocedural orientation and to assess the extent of tumour resection.[6-9] But its application to transsphenoidal surgery is notably limited by the size of its probes, and by the fact that later probes – having adopted a side-viewing design precisely in an attempt to reduce their size – produce images that are more difficult to interpret intraoperatively.[10, 11] To both these ends, we have developed a slender, forward-viewing ultrasound device for transsphenoidal access and plan to create novel software tools to integrate this device into a surgical navigation system. It is hoped that this integrated system will be helpful in locating residual pituitary tumour tissue as well as neurovascular structures. Building upon our pre-clinical experience with the probe on phantom heads,[12] the purpose of the current study is to confirm the feasibility and safety of this new intraoperative ultrasound device in an initial patient cohort. As such, the work presented here is at stage 1 (Idea phase) of the "Innovation, Development, Exploration, Assessment, and Long-Term Study (IDEAL) model" statements.[13]

Method

Ethical approval was obtained from our local ethics committee (19/LO/0882), and the trial was registered on ClinicalTrials.gov (NCT03284775).

Study design

A single-centre prospective proof of concept study design was adopted, as defined by the IDEAL guidelines for assessing innovation in surgery, and the relevant reporting guidelines were used in the preparation of this manuscript.[13, 14]

The study began in October 2019 and involved patients undergoing transsphenoidal surgery for pituitary adenoma at the National Hospital for Neurology and Neurosurgery.

Participants

The minimum inclusion criteria were 1) adult patients, 2) undergoing transsphenoidal surgery, 3) diagnosis of pituitary adenoma on pre-operative MRI, and 4) able to provide consent. The patients recruited were highly selected, and we favoured patients with more normal anatomical configurations and standard pathological appearances.

All patients gave their written informed consent to test our ultrasound probe after the risks, benefits, and alternatives were discussed. Patients were specifically informed that this was the first clinical application of this novel ultrasound probe.

Patients were recruited from October 2019 to March 2020, when the UK entered a lockdown in response to the COVID-19 pandemic. All operations were performed by IC, HJM, and NLD, who have a subspecialty interest in pituitary surgery, and were involved with the design and preclinical assessment of the ultrasound probe. All operations took place at the National Hospital for Neurology and Neurosurgery, which is a large regional neuroscience centre, that carries out approximately 150-200 pituitary operations each year.

Intervention

Our quasi-forward-looking ultrasound probe is shown in Figure 1. It is a clinical-grade prototype manufactured by Vermon (Vermon S.A., Tours, France) based on design requirements stemming from our research team. Vermon is a company specialising in advanced transducer technologies. The probe's design corresponds to a novel version of two previous prototypes, which were also manufactured by Vermon and used successfully for patients undergoing transsphenoidal surgery.[12,13] Our novel transducer consists of an endoscopic-shaped probe with a shaft that is slenderer than in previous versions. The tip is 200 mm long and has a diameter of 7 mm. At the end of the probe, an 80-element convex array with a

curvature radius of 8.48 mm is located along the tip, imaging both in the forward and side directions. The centre frequency is higher than previous prototypes, 18 MHz, to improve image resolution. The transducer's connector is compatible with the CE-marked SonixTouch ultrasound console (BK Ultrasound, UK). The ultrasound probe is cleaned before and after use using standard wet wipes, and is gelled and draped in the usual fashion during surgery (Molnlycke Healthcare, UK).

The surgical technique for the endoscopic transsphenoidal approach is unchanged to that used without the ultrasound probe. General anaesthesia is administered, and nasal mucosal decongestants applied (Moffat's solution). Patients are positioned supine, in the conversational position,[15] and the operative field prepared and draped in a sterile fashion. Access to the sella turcica is performed through a mononostril endoscopic approach. If needed, the floor and anterior wall of the sella are drilled off. A cruciate incision is made to the dura mater and the tumour removed using curettes and rongeurs. The ultrasound probe is applied to the sella before and after the dural incision for visualisation of the tumour and surrounding neurovascular structures. Haemostasis is achieved using bipolar electrocautery, Spongostan (Ethicon, Johnson & Johnson) or Surgiflo (Ethicon, Johnson & Johnson). In case of an intraoperative cerebrospinal fluid (CSF) leak, a fat graft is harvested from the patient's abdomen and placed over the dural defect. Nasal packing is not placed in the absence of CSF leak.

Measures of outcome

The primary outcomes of the study were to demonstrate that the use of the ultrasound device in pituitary surgery is both technically feasible and safe. Technical feasibility was assessed by the ability of the probe to be used during transsphenoidal surgery alongside standard surgical equipment. Device safety was assessed by the number, type, and severity of adverse events related to use of the device, e.g. device malfunction.

The secondary outcomes were to demonstrate that the ultrasound device does not adversely affect the occurrence of postoperative complications, the operating time (minutes), and the length of stay (days). For this purpose, the operating times and length of stay were also collected for a series of 30 consecutive patients with pituitary adenoma, operated before and contemporaneously to this study, by the same surgical team and with the same surgical technique, but in whom intraoperative ultrasound had not been used. Postoperative complications to be recorded included death, cerebrospinal fluid leak, meningitis, vascular

complications, visual complications, diabetes insipidus, hypopituitarism, and cranial nerve injury. Vascular complications to be recorded included carotid or other vessel injury, or symptomatic haematoma. Venous bleeding from the cavernous sinus was to be considered a vascular complication only if it prevented completion of the surgical procedure. Epistaxis was only to be considered a vascular complication if it warranted return to the operating room. Cerebrospinal fluid leaks to be recorded included all postoperative leaks requiring lumbar drainage or repair. Patients with Cushing's disease receiving postoperative cortisol, or in whom a hypophysectomy was carried out were also not included as surgical complications.

A short written assessment of the probe usage was performed by the surgeon carrying out the procedure after each operation.

Results

Baseline data

Eleven patients were approached to participate in this study and all eleven were recruited, but only five participated (2 female, 3 male; age range: 42–73 years), due to the study's discontinuation in the general response to the COVID-19 pandemic. Diagnosis was gonadotroph pituitary macroadenoma in three cases, acromegaly in one case (somatotroph pituitary microadenoma), and a haemorrhagic cystic residual of a previously resected gonadotroph macroadenoma in the remaining case.

Intervention and outcomes

Primary outcomes

The probe's ability to be used alongside the standard surgical equipment for transsphenoidal procedures (Figure 2A) was demonstrated in all cases. Once the sella turcica is entered, we usually fix the endoscope, using its holder, in the supero-external angle of the sphenoid opening for the greater part of the procedure, allowing bimanual handling of instruments in and around the pituitary fossa. Our ultrasound probe could be handled in the same way as another instrument, under endoscopic vision and without entering into conflict with the endoscope in all five cases (Figure 2B).

No adverse events related to the device were encountered.

Secondary outcomes

Following discharge, one patient represented with a delayed CSF leak in the context of an acute abdominal obstruction and subsequently developed meningitis. None of the patients had new pituitary hormonal deficits postoperatively, aside one patient who remained on hydrocortisone replacement therapy on follow-up.

Operating time ranged from 68 to 110 minutes (mean: 93 min) and length of stay was 4 days in one case, 5 days in two cases, 6 days in one case and 18 days in the case with acute abdominal obstruction (median: 5 days). This represents a 20 min difference when compared to the average operating time of thirty contemporaneous, consecutive cases of pituitary adenoma resection performed by our team without intraoperative ultrasound (range: 45–168 min, mean: 73 min). The length of stay for this same group, on the other hand, was comparable (range: 2 – 20 days, median: 4 days).

Three written assessments positively underlined that tumour and vessels were readily identifiable, and in two cases that an adenoma residual was evident. In one of these cases, ultrasound allowed to identify a residual that would not have otherwise been noticed. Additional remarks were that ultrasound clarity was best before opening the dura mater, that flowable haemostatic matrix obscured the view and that the Doppler overlay was useful for a better distinction of the structures dorsal to the tumour. One assessment observed that the probe would be best used alongside neuronavigation, in view of the difficulty to convincingly identify the anatomy on ultrasound in that particular case.

Discussion

Principal findings

The present study shows that the use of our novel ultrasound device, specifically developed for the transnasal corridor to the pituitary gland, is both technically feasible and safe.

We did not encounter any adverse effects in this preliminary cohort. The use of the ultrasound probe did not significantly disrupt the surgical workflow and the additional average surgical time compared favourably with scanning times reported for other intraoperative imaging modalities.[16-18] We did however experience some difficulty with flattening the superfluous folds of the probe's protective sterile sheath, actually intended for bulkier probes and so adding

unwanted volume to our prototype (Figure 2B). This led to the aggregation of air bubbles near the tip of the probe, causing the formation of reflection artifacts in the image (Figure 4C). We rapidly learned to make use of a sterile elastic band to maintain the sheath taut around the probe's tip (Figure 2A). Nevertheless, a dedicated slimmer sheath or a transducer design compatible with standard sterilisation processes would be a preferable solution for future use. Finally, the probe did not enter into conflict with the endoscope, which was positioned superolaterally in the ipsilateral nostril, and so could be introduced under direct endoscopic vision (Figure 2B).

Operator feedback collected following surgery conveyed that vessels and tumour contours were readily identified on ultrasound (Figures 3 & 4); that clarity was felt to be best before opening the dura mater; and that the use of flowable haemostatic matrix obscured the ultrasound views. Although our project is not yet at a phase to assess our probe's intraoperative impact on surgical decision-making, anecdotally it did allow to identify an adenoma residual in one patient that would otherwise have been missed.

Relation to other studies

Our prototype is less bulky than another recent forward-viewing probe, which was found to be too large to safely enter the sphenoid sinus in 2 patients of the 24 included in that report.[11] The same group reported six years earlier on their experience with a slenderer prototype, where the transducer was side-viewing, but where the ultrasound images were also less intuitive as a consequence.[10] Side-viewing designs have since become commercially available. Indeed, the development of thin ultrasound probes, dedicated to the transsphenoidal approach, has been based on a necessary trade-off between image quality (which is dependent on the number of ultrasound elements, greater in the side-viewing prototype) and image intuitiveness (best in the forward-viewing probe). Moreover, a side-viewing probe needs to be inserted *into* the sella turcica to be able to scan the sellar structures, thereby limiting its use to larger tumours, where an initial cavity has to first be made for the probe's tip to be introduced.[10, 11, 19] In contrast, a forward-viewing probe does not have to enter the sella to scan it.

It is with these surgically relevant considerations that we decided to centre further development around a forward-viewing prototype, and to work on optimising image quality for the purpose of transsphenoidal surgery while at the same time keeping the probe's diameter in proportion with the surgical corridor. Accordingly, our prototype has a diameter of 7 mm, in contrast to

the 12 x 8 mm rectangular tip of the previously reported forward-viewing probe discussed above.[11] The transducer's array also has a higher central frequency, 18 MHz, as compared with the transsellar and intrasellar probes, which exhibit a central frequency of 10.3 MHz and 12 MHz, respectively. The number of piezoelectric elements was raised to 80 and the pitch size reduced to 100 μm to mitigate the appearance of grating lobes artifacts, as suggested by Solheim et al.[10] The miniaturisation of the linear convex array allowed us to place it in the forward-looking direction and provide more familiar imaging planes.

The high frequency of our transducer provides high-resolution images but also affects the imaging depth due to the generation of pulses of shorter wavelength, which are more attenuated in tissue. However, we did not require an imaging depth greater than 4 cm during surgery, and the effect of attenuation on the image quality was negligible. Furthermore, the probe's resolution was assessed in a previous experiment[12] and consisted in imaging a 25 μm tungsten fibre at different depths in a water bath. The average resolution of our transducer across depth (from 0.5 cm to 2.5 cm with intervals of 0.5 cm) was measured to 0.26 mm (± 0.02) in the axial plane and 1.3 mm (± 0.3) in the lateral plane.

Strength and limitations

The strength of this report is its continuity with previous pre-clinical work, ensuring that the surgical team, who had also been involved in the protoype's design, already had a good working knowledge of the system for the purpose of the IDEAL stage 1 assessment intended in this study.

Although an IDEAL stage 1 study is intended as a proof of concept and is therefore usually limited to a small number of patients, our cohort was in fact smaller than we had initially planned due to the study having been suspended in the wake of the COVID-19 pandemic. This point can be advanced as a limitation to the descriptive nature of this report.

Conclusion

Our study demonstrates the safety and feasibility of our ultrasound probe during transsphenoidal approaches to the pituitary fossa. An IDEAL stage 2a (Development phase) is now planned to integrate this device into a surgical navigation system, as a means of further enhancing the intraoperative understanding of the surgical field.

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Figures

Figure 1. Photograph showing the novel forward-viewing ultrasound probe. **(A)** 200 mm. **(B)** 15 mm. **(C)** 85 mm. The probe tip's diameter (the distance between the **two blue arrows**) is 7 mm. **(D)** The probe's distal 16 mm contain an 80-element convex array. The radius of the transducer's curvature (**indicated by black arrowhead**) is 8.48 mm.

Figure 2. (A) Photograph of the surgical field showing the ultrasound probe in use alongside the endoscope. **(B)** Top view: Transsphenoidal endoscopic view through left nostril showing the opening made in an enlarged sella turcica. The pituitary tumour has been partially resected. Middle view: The sphenoid sinus is filled with water to reduce acoustic impedance. Lower view: The ultrasound probe's tip is inserted through the sellar opening under endoscopic vision.

Figure 3. (A) T2-weighted coronal magnetic resonance imaging slice of a patient with a pituitary macroadenoma with suprasellar expansion causing displacement of the optic chiasm. The inset in the top right corner of panel A is a T1-weighted sagittal slice in the same patient indicated the level of the coronal slice (thin blue line). The white rectangular frame centred on the tumour's apex, seen protruding through the diaphragm sellae, provides the approximative bearings of panel B, whilst the oblique frame centred on the cavernous segment of the right internal carotid artery provides the bearings for panel C. **(B)** Intraoperative ultrasonographic caption showing the suprasellar portion of the tumour, protruding through the diaphragm sellae. The diaphragm sellae is indicated on either side of the tumour by arrowheads. The hypoechogenic space dorsal to the tumour represents the posterior aspect of the suprasellar cistern, just posterior to the optic chiasm and the pituitary stalk. This ultrasound caption is therefore an oblique slice that represents structures slightly posterior to those shown in panel A, i.e. it shows the tumour apex as it begins its posterior descent (see inset in panel A). **(C)** Intraoperative ultrasonographic caption of the right infrasellar portion of the tumour. The right diaphragm sellae is indicated by the white arrowhead. The asterisk indicates the cavernous segment of the right internal carotid artery. Note the heterogenous "mottled" tumour echogenicity visible in panels B and C, and corresponding to the intratumoural regions of T2 hyperintensities seen in panel A.

Figure 4. (A) T2-weighted coronal magnetic resonance imaging slice of a patient with a pituitary macroadenoma with suprasellar expansion causing compression of the optic chiasm.

The inset in the top right corner of panel A is a T1-weighted sagittal slice in the same patient indicated the level of the coronal slice (thin blue line). The white rectangular frame centred on the cavernous segment of the left internal carotid artery provides the approximative bearings of panel B, whilst the left frame centred on the tumour's apex provides the bearings for panel C. **(B)** Intraoperative ultrasonographic caption of the left lateral aspect of the tumour and of the cavernous segment of the left internal carotid artery (asterisks). **(C)** Intraoperative ultrasonographic caption showing the suprasellar portion of the tumour. The A1 segment of the left anterior cerebral artery has been sliced longitudinally. Its dorsal wall is the faint hyperechogenic line shown by the full white arrowhead. The contralateral A1 has been sliced transversally and slightly obliquely, and can be made out faintly as an ovoid circle (hollow arrowhead). The tumour is mostly of a homogenous appearance both on panels B and C. Panel C is also illustrative of reverberation artifact, due to the presence of air between a segment of the convex ultrasound array and the medium.

Figure 1

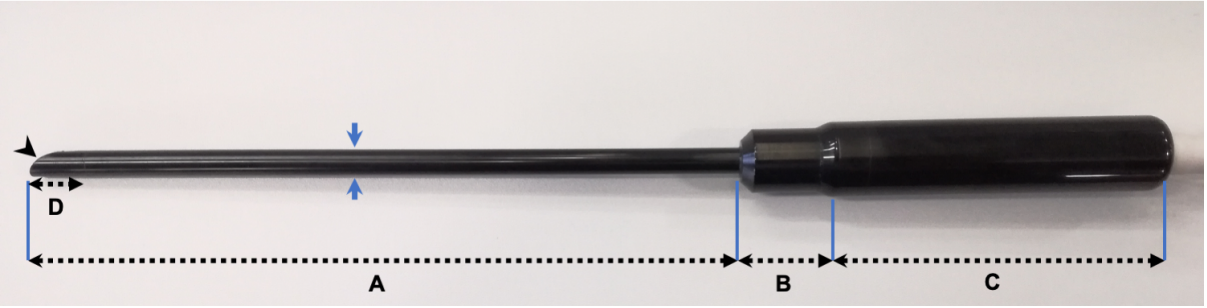

Figure 2

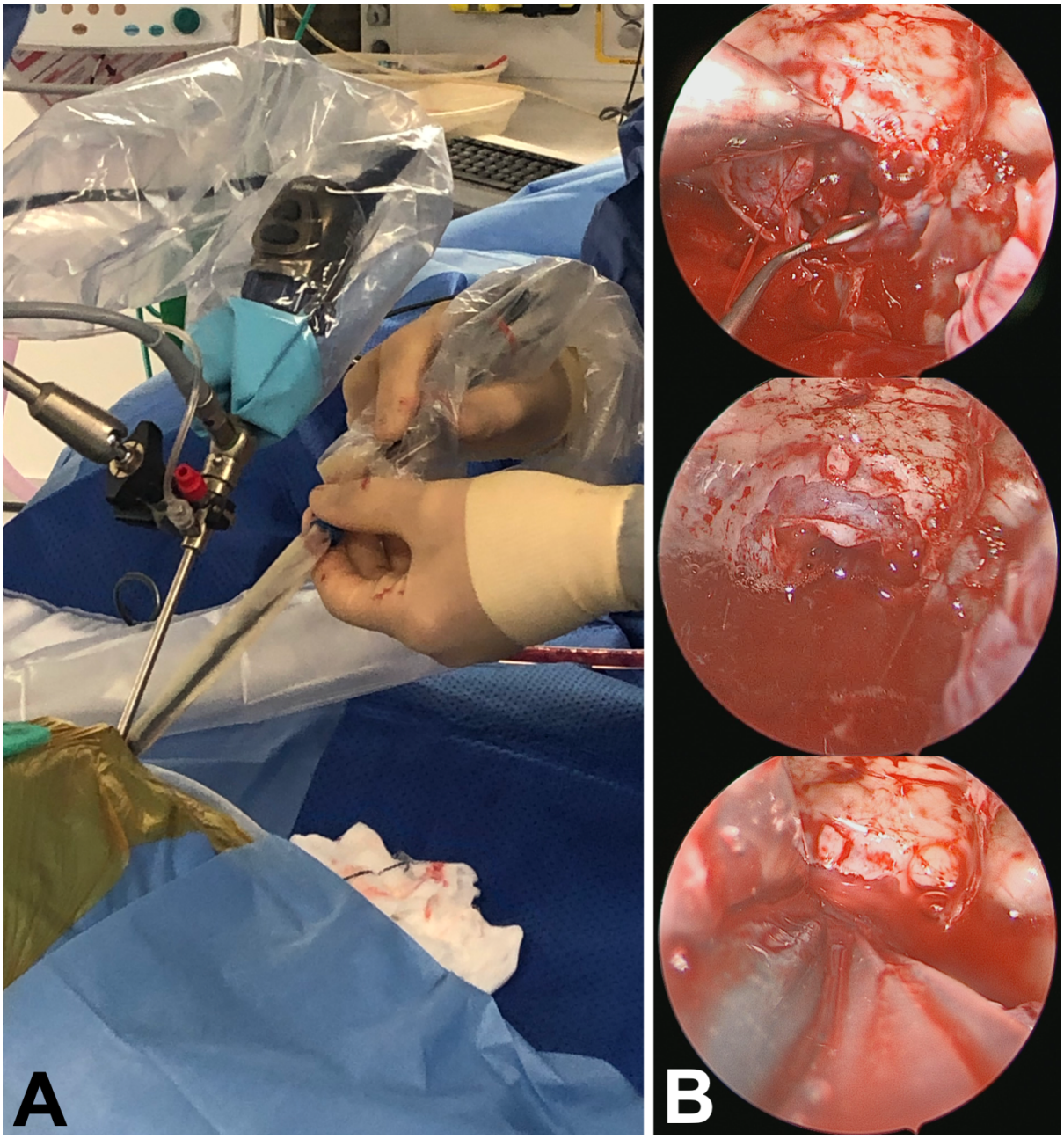

Figure 3

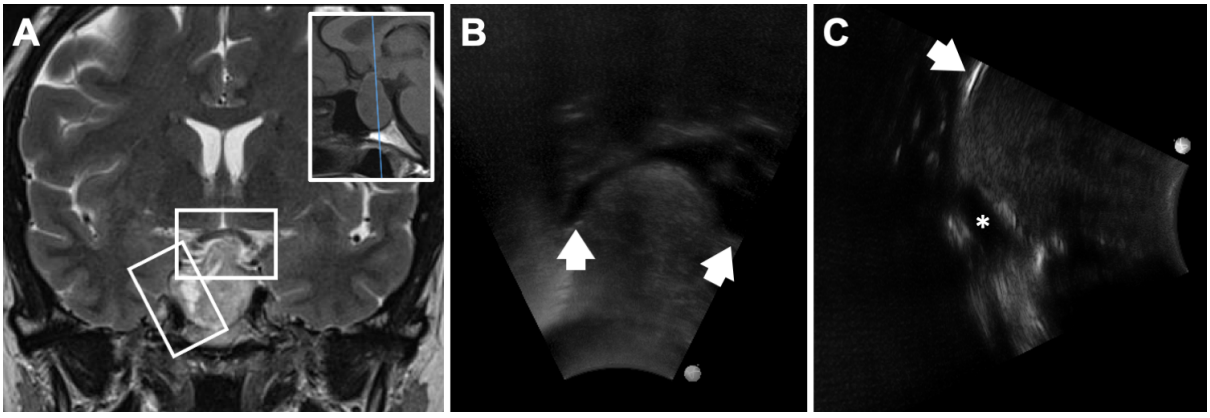

Figure 4