

Manuscript title:**Depicting the sphenopalatine ganglion on 3 Tesla magnetic resonance images****Abstract:**

Objective: The sphenopalatine ganglion has yet not been identified on medical images in living humans. The primary aim of this study was to evaluate whether the SPG could be identified on 3 Tesla MR imaging.

Methods: This study was performed on medical images of 20 Caucasian subjects (40 sides, n=40) with an exploratory design. 3 Tesla MR images were assessed by two observers for the presence and size of the sphenopalatine ganglion. The distance from the sphenopalatine ganglion to four bony landmarks was registered from fused MR and CT images. In an equivalence analysis the distances were compared to those obtained in an anatomical cadaveric study as historical controls (n=50).

Results: A structure assumed to be the sphenopalatine ganglion was identified on MR images in all patients on both sides by both physicians. The mean size was depth 2.1 ± 0.5 mm, width 4.2 ± 1.1 mm and height 5.1 ± 1.4 mm, and is in agreement with formerly published data. Equivalence of the measurements on MR images and the historical control was established, suggesting that the structure identified on MR images is the sphenopalatine ganglion.

Conclusion: Our findings suggest that the sphenopalatine ganglion can be detected on 3 Tesla MR images. Identification of this structure may be important in image guided interventions targeting the sphenopalatine ganglion, and can hopefully increase efficacy, safety and reliability for these treatments.

Keywords

Magnetic resonance, MRI, sphenopalatine ganglion, pterygopalatine ganglion, surgical navigation, image guidance.

Main body

Introduction

The sphenopalatine ganglion (SPG) is an autonomic cranial ganglion situated in the sphenopalatine (pterygopalatine) fossa and represents the second largest neural structure of the head. It carries sensory, sympathetic and parasympathetic nerves that innervate structures of the head and the face and is a target for interventional treatment for a range of disorders including headaches, atypical facial pain, trigeminal neuralgia, allergic rhinitis, and sinonasal polyps (1, 2). The size of the human SPG has been measured by Vogel to height 3-4 mm, width 2-3 mm, and depth 1-2 mm (3). Due to the localisation deep in the head image guided methods such as medical image guidance or surgical navigation are needed for accurate and safe performance, but the SPG has yet not been identified on medical images in living humans. Variation of the localisation of the SPG is a proposed reason for failures in techniques targeting the SPG (4). Accuracy, safety and reliability may be improved in image guided procedures if SPG can be identified on routine medical images. During the development of a novel technique of injection of onabotulinumtoxinA towards the SPG using surgical navigation and a novel device, a need for the exact localisation of the SPG arose. In two pilot studies exploring the safety of this injection for the treatment of chronic cluster headache (n=10) (5) and chronic migraine (n=10) (6), CT

and magnetic resonance imaging (MRI) were performed for the preplanning of the procedure.

Lang and Keller (7) performed an anatomical dissection of 50 half heads, 38 males and 12 females, measuring the distances with callipers from the SPG to the mid-sagittal plane, conchal crest, and the centres of the anterior aperture of the vidian canal and foramen rotundum. This is the largest study we have been able to find identifying the location of the SPG in relation to structures easily identified on CT and may therefore be suitable to establish equivalence with our findings. Only mean distance and range are given in the publication, but, fortunately, in the doctoral thesis of Keller the results of the same study are given with variance of the mean (8), enabling us to do an aggregated statistical comparison of our measurements on MRI with the same measurements on cadavers by Lang and Keller as a historical control. By the concept of trilateration, a process where the location of one point in a three-dimensional space can be determined by the distance to other multiple points, the location of the SPG on living humans measured on MRI can be compared to the location on cadavers measured with callipers.

The primary aim of this study was to evaluate whether the SPG could be identified on MRI. An equivalence analysis of the distance between the assumed SPG to multiple

landmarks on fused MR and CT images with those obtained from an anatomical study on cadavers as a historical control was performed to support our findings.

Method

The present study was performed on medical images of 20 Caucasian subjects (40 sides, n=40) participating in two pilot studies evaluating the safety of injection of onabotulinumtoxinA towards the SPG using surgical navigation. One study was performed on chronic cluster headache (n=10), and one on chronic migraine (n=10), both conducted at St. Olavs Hospital, Trondheim, Norway, between October 2013 and February 2016. The studies were approved by the regional ethics committee (ref. 2012/164 and 2014/962), the Norwegian Medicines Agency (EUDRACT nr: 2012-000248-91 and 2014-001852-43) and registered at ClinicalTrial.gov (NCT02019017 and NCT02259075). Written informed consent was obtained from all patients. Unenhanced CT and MRI were performed on all participants covering the region of the sphenopalatine fossa and its vicinity.

MR scans were performed on a 3T scanner (Magnetom Skyra, Siemens, Germany). Technical parameters for MR scans were as follows: Sagittal T2 weighted: Repetition time (TR) range 3780, echo time (TE) 111, slice thickness 2 mm, matrix 0.4x0.4x2.0 mm, field of view (FOV) 210, number of acquisitions 3; sagittal T1 weighted: TR

range 710, TE 10, slice thickness 2 mm, matrix 0.4x0.4x2.0 mm, FOV 210, number of acquisitions 2; axial T2 weighted: TR range 4160, TE 110, slice thickness 2 mm, matrix 0.4x0.4x2.0 mm, FOV 220, number of acquisitions 2; and axial T1 weighted: TR range 710, TE 7.9, slice thickness 2 mm, matrix 0.4x0.4x2.0 mm, FOV 210, number of acquisitions 2. All CT scans were performed using a helical CT scanner (Somatom sensation 64, Siemens, Germany) set at 63 mA, 120 kV and 1mm slice thickness. The MRIs were assessed independently by two observers for the presence and size of the SPG on Sectra Workstation IDS7 (Sectra AB, Sweden), then reviewed together were differences of opinion were resolved by consensus. Three measurement of the size of the SPG were registered: Width was defined as the largest measure in parallel of the nearest posterior bone of the SPG in the axial plane; depth as the largest measure perpendicular to the width in the axial plane; and height as the largest measure in the sagittal plane. Fusion of MR and CT images was performed using Brainlab iPlan 3.0 (Brainlab AG, Feldkirchen, Germany). For identification of bony landmarks the CT images were reconstructed using a bone algorithm and evaluated at bone (wide) window setting. The CT images were reviewed together by two physicians and coordinates for the SPG and the landmarks were registered. Coordinates of the following landmarks were registered: Foramen rotundum; vidian canal; mid-sagittal plane; and conchal crest (posterior part). The coordinates of the nearest bony point of the anterior and posterior limitation of the sphenopalatine fossa

in relation to the SPG were also obtained. The centre of the SPG and the centre of the anterior aperture of foramen and canals were used as point for measurements. The mid-sagittal plane was set by visual evaluation of the anatomy. Distances between landmarks were calculated using the coordinates of the SPG and landmarks.

To confirm our findings on MRI, distances from SPG to the bony landmarks were compared to those obtained by Lang and Keller in an anatomical cadaveric study on 50 cadaveric half heads ($n=50$) (7, 8) as a historical control.

Statistical analysis

SPSS version 21.0 (SPSS Inc., Chicago, Illinois, USA) was used in the data analyses. Data distributions were expressed as means and standard deviations (SD), results are given as mean \pm standard deviation if not otherwise stated. Due to the exploratory nature of the study, sample size calculation was not performed. Aggregated data was used to calculate the difference of means with a two-tailed 95% confidence interval for each measured distance on MRI compared to the historical control. To our knowledge, there is no available data for comparisons of these two methods of measurements. In the absence of published data, a pre-specified equivalence margin of 3 mm was selected because we consider a smaller difference as irrelevant in comparing these two methods of measurement.

Results

Demographics are given in Table 1.

MRI

A structure assumed to be SPG was identified on MRIs in all patients on both sides by both physicians. Differences of opinion were encountered in 11 sides. In all 11 sides, it was decided by consensus that one of the physicians had misjudged the cross-section of the maxillary nerve as the SPG, in all cases being to lateral and superior for the expected location of the SPG. In most cases SPG was easiest to identify on axial T1 weighted sequences, and none was identified on coronal slides. We found that the easiest way to detect the SPG was to first identify the vidian canal, which in most cases can be identified on MRIs due to the characteristic wide anterior opening. The most typical location of the SPG is on the lateral side of the vidian canal as it opens into the sphenopalatine fossa. The SPG was identified in this approximate location in 29 sides. The most typical shape of the SPG in the axial plane was a crescent shape (Figure 1) seen in 29 sides, on 8 sides it was more rounded and in 3 sides elongated. The signal intensity of the SPG on both T1 and T2 weighted images was intermediate as expected for neural structures. The mean size of the SPG was depth 2.1 ± 0.5 mm, width 4.2 ± 1.1 mm and height 5.1 ± 1.4 mm.

Fused MR and CT images

Table 2 depicts distances from SPG to bony landmarks and the same measurements obtained by Lang and Keller on 50 cadaveric half heads (50 sides). Since all upper and lower boundary of the two-sided 95% confidence interval lay within the equivalence margin, equivalence of the distance from the SPG to the landmarks were established. The average distance from the centre of the SPG to the nearest point of the bony anterior and posterior limitation of the sphenopalatine fossa were respectively 3.3 ± 1.3 mm and 1.6 ± 0.5 mm. The SPG was located on average 3.3 ± 1.1 mm (range: 0.9-5.6) anterior, 2.8 ± 1.2 mm (range: 0.5-4.8) lateral and 1.3 ± 1.3 mm (range: -1.5-5.6) inferior to the centre of the anterior aperture of the vidian canal.

Discussion

A structure assumed to be SPG was identified in all 40 sides on 3 Tesla MRI. The size of the structure was measured to be depth 2.1 ± 0.5 mm, width 4.2 ± 1.1 mm and height 5.1 ± 1.4 mm, which is in compliance with the literature (3, 9, 10). The mean difference calculated by comparing the relative location of the SPG to four bony landmarks in medical images in our study with the same measurements performed in an anatomical study of 50 half heads were small, but significantly different for the distance between the SPG and the mid-sagittal plane, the conchal crest and the foramen rotundum. A

statistical significant difference on a 5% level was not found for the distance between the SPG and the vidian canal. The two methods of measurements are different, one on medical images of living humans using coordinates to calculate distances and the other on cadavers using callipers, so neither a statistical significant difference nor a lack of statistical significant difference can prove equivalence (11). The upper and lower boundary of the two-sided 95% confidence interval lay within the pre-specified equivalence margin of 3 mm for all four measurements, hence equivalence of the measurements on MRI and the historical control was established, suggesting that the structure identified on MRI is the SPG.

The most common misjudgement during the examination of the MRIs was mistaking the maxillary nerve as it enters the sphenopalatine fossa. The maxillary nerve emerges from the foramen rotundum and turns medially to enter the sphenopalatine fossa and then, after giving off the sphenopalatine nerves, leaves the fossa superiorly through the inferior orbital fissure. Hence, an axial view of the maxillary nerve as it enters the sphenopalatine fossa in a horizontal direction may give the impression of a larger structure than expected. This structure was in all cases both superior and lateral to the SPG.

We found that the easiest way for us to detect the SPG on MRI was to identify the vidian canal on axial slices. The SPG was in approximately three quarters of the images located near the lateral aspect of the opening of the vidian canal in the sphenopalatine fossa. Typically it has a crescent shape in the axial plane (Figure 1).

Oomen et al performed 7 Tesla MRI of one cadaver head and was able to detect the SPG, the location was verified by dissection (12). 7 Tesla MRI are still rarely used in routine clinical practice, and image appearance is affected by cadaver preparation. The authors refers to an article by Chang et al on imaging of malignant melanoma of the head and neck stating that the SPG can easily be identified, but the SPG is not mentioned in the referenced publication (13). In 2007 Alvernia et al published the results of MRI and CT imaging of three patients scheduled for gamma-knife treatment targeting the SPG (10). They concluded that SPG could not be identified on MRI.

The knowledge of the anatomy of the SPG is based on few anatomical studies (4). The SPG is pyramid shaped with a mean diameter of 3,5 mm (10). It is suspended from the maxillary nerve by the sphenopalatine nerves. SPG is situated in the sphenopalatine fossa shaped as a pyramid up-side down in both the coronal and sagittal plane. The sphenopalatine fossa has the following boundaries (14); superiorly with the infraorbital fissure, laterally with the pterygomaxillary fissure, medially with the

palatine bone, posteriorly with the pterygoid process, anteriorly with the posterior wall of the maxillary sinus and inferiorly with the palatine canal. Additionally, it communicates with the nasal cavity through the sphenopalatine foramen, the middle cranial fossa through foramen rotundum and the foramen lacerum through the vidian canal. Sphenopalatine fossa is divided into three compartments; an anterior compartment carrying mainly blood vessels, a central compartment of adipose tissue and a posterior compartment containing mainly neural structures including the SPG.

The nasal cavity, the paranasal sinuses and the lacrimal gland are innervated by autonomic fibres from the SPG. Additionally, there is evidence of parasympathetic innervation of intracranial structures through the SPG (15, 16). Based on this knowledge, the SPG has been targeted for the treatment of a wide range of disease entities including headache, facial pain, sinusitis and rhinitis (1, 2).

Targeted interventions towards the SPG for the treatment of primary headaches include radiofrequency destruction, neurostimulation and injections. Two different techniques for guidance are frequently reported; fluoroscopy and CT guidance. The SPG cannot be seen on the medical image when using either of these two techniques. . We posit that performing a pre-treatment MRI may give the precise location of the SPG, and this data can be used, either by image fusion or landmarks measurement, to

increase the accuracy of the treatment. For insertion of stimulation electrodes, accuracy is important for both effect and decreasing the incidence of unintended stimulation of nearby sensory nerves inducing paraesthesia. The exact localisation of the SPG in each case may increase accuracy of insertion.

Several studies report the results of injection towards the SPG, including chemical destruction with alcohol or phenol (17) and short-acting local anaesthetics in combination with corticosteroids (18). The authors of the present study have recently published the first reports of onabotulinumtoxinA injections towards the SPG in intractable chronic cluster headache and chronic migraine (5, 6). To achieve the accuracy necessary to perform such blockade the procedure was performed with a surgical navigation assisted technique. Surgical navigation is a system of widespread use that tracks and displays the tip of an instrument relative to a pre-required medical image. CT-guidance to perform injections towards the SPG seems feasible, but, in the cases of repeated injections, it raises the question of radiation hygiene, both for patient and the interventionist. By using surgical navigation, one CT acquisition may be used for repeated injections over time, alleviating the concerns of radiation hygiene. Another advantage of surgical navigations is the possibility of fusion of MRI and CT, and as such transfer the exact location of the SPG to CT images, enabling the interventionist to see the location of the SPG during the procedure. This technique was

applied in the abovementioned studies of onabotulinumtoxinA injections towards the SPG.

Limitations

In the present study we aimed at identifying a structure on MRI that has not been identified before in living humans. The evaluation of the MRIs was based in consensus between the examiners, and evaluation of an inter-observer agreement was not appropriate with this exploratory design. Only two physicians examined the images. All patients had primary headache, but there is no evidence of deviance of the anatomy of the head in this population. A comparison of the results was performed with measurements from a cadaver study that do not state the race of the subjects. In the cadaver study 24% of the subjects were females, compared to 75% in the current study. Due to different mean skull size in males and female and between different races, this may have biased the results. In a post-hoc analysis we could not find a trend towards sex dependent differences of the measured distances in our material. Sample size calculation was not performed due to absence of published data on the method. There are methodological differences in the current study and the historical data, especially concerning the methods of measurement, and published data to support the equivalence margin determination was not found. The margin was set merely on a constancy assumption based on the investigators judgment. This study should be

considered an exploratory study and the results should be confirmed by further investigations on a larger population, with more examiners and establishing an inter-observer correlation.

Conclusion

Our findings suggest that the SPG can be identified on 3 Tesla MRIs with the presented imaging protocol. By comparing the relative location of the SPG to bony landmarks in medical images in our study with those obtained in an anatomical cadaveric study as a historical control we find that the distances from the SPG to four bony landmarks are equivalent, establishing as probable that the structure identified on the MRI is the SPG. Identification of the SPG may be important in image guided interventions targeting the SPG, and has the potential to increase efficacy, safety and reliability for these treatments.

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Conflicts of interest

The results of this study may affect opinions on the feasibility of interventional treatments targeting the SPG. An intervention device for image guided injections of pharmacological substances towards the SPG is developed at NTNU and St. Olavs Hospital, Trondheim University Hospital. These institutions may benefit financially of a commercialization of the device through future possible intellectual properties, this may include financial benefits to authors of this article. Dr. Bratbak is co-inventor of a proposed treatment targeting the SPG and the intervention device used to perform the treatment, both inventions patent pending, and may benefit financially of a commercialization of the proposed treatment through future possible intellectual properties. Dr. Folvik has nothing to disclose. Dr. Nordgård is co-inventor of a proposed treatment targeting the SPG and the intervention device used to perform the

treatment, both inventions patent pending, and may benefit financially of a commercialization of the proposed treatment through future possible intellectual properties. Dr. Stovner has nothing to disclose. Dr. Tronvik may benefit financially of a commercialization of a proposed treatment targeting the SPG and the intervention device used to perform the treatment through future possible intellectual properties.

Clinical Implications

- Our findings in this exploratory study suggest that the SPG can be identified on MRIs with the presented imaging protocol.
- By comparing the distances between the assumed SPG and four landmarks in the current study with a historical control of measurements on cadavers establish equivalence of the results, suggesting that the structure identified on the MRI is the SPG.
- The clinical implication of these findings is that targeting the SPG with medical image guidance for injection, stimulation or destruction, may be performed with better accuracy and precision.

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