Preliminary exploration of functional MRI in sinonasal paragangliomas

Graphical abstract

Key points
This study evaluated the functional imaging of sinonasal paragangliomas (SNPGs) and demonstrated that the apparent diffusion coefficient (ADC) values of SNPGs might be higher than those of other sinonasal malignancies and the characteristic succinate peak helped with the diagnosis of SNPGs.

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Preliminary exploration of functional MRI in sinonasal paragangliomas

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Abstract

Objectives: This study was aimed at evaluating functional MRI combined with conventional MRI as well as CT imaging in the diagnosis of sinonasal paragangliomas (SNPGLs).

Methods: Clinical data, CT imaging, conventional MRI, and functional MRI findings of four patients with pathologically confirmed SNPGLs were reviewed retrospectively. Multi-parametric functional MRI features were analyzed, including diffusion-weighted imaging (DWI), dynamic contrast-enhanced imaging (DCE), and proton magnetic resonance spectroscopy (1H-MRS). An ADC map was generated through DWI, and the values of the lesions were measured. A time-signal intensity curve pattern was obtained through DCE. Peaks for biological compounds were derived from 1H-MRS.

Results: Three patients underwent DWI examination. DCE was also available in two patients, and 1H-MRS was performed in one patient. The ADC value obtained from DWI was higher than 1.0×10⁻³ mm²/s in all patients, and DCE presented a type III or type II pattern. A characteristic succinate peak and a high ratio of choline to creatine were also detected through 1H-MRS.

Conclusions: Imaging features on multi-parametric functional MRI reflected the histopathological microenvironment within SNPGLs, and might aid in the diagnosis of SNPGLs in combination with conventional imaging.

Keywords: paragangliomas, sinonasal, CT, MRI, diagnosis

1. INTRODUCTION

Paragangliomas are rare neuroendocrine tumors derived from neural crest cells that located outside the adrenal glands. They are usually distributed along the paraganglia, and approximately 3% occur in the head and neck region [1]. The most recent edition of the WHO Classification of head and neck tumors suggests that paragangliomas have undetermined biologic potential and should not be considered benign [2]. Sinonasal paragangliomas (SNPGLs), which are located in the nasal cavity and paranasal sinus, are rarely found, and approximately 50 SNPGLs have been reported to date [1]. The appearance of SNPGLs under conventional CT and MRI has been published in several case reports [3-10]. These noninvasive methods have played key roles in both tumor localization and the identification of local invasion as well as metastasis. CT primarily indicates erosive bone changes in SNPGLs, such as bony destruction of the skull base and the walls of the sinuses [11], whereas MRI shows the invasive involvement of adjacent structures, including the cranial fossa, the sinuses, or the turbinates [12]. Furthermore, “salt and pepper” signs on MRI T1WI and T2WI have also been considered to be a specific appearance of SNPGLs [13]. However, such bony destruction and invasive involvement of the adjacent structures may also be present in other sinonasal malignancies, such as sinonasal carcinomas, esthesioneuroblastoma, and melanoma [14-16]. The “salt and pepper” sign is not pathognomonic, because it can also be observed
Multi-parametric functional MR techniques, including diffusion-weighted imaging (DWI), dynamic contrast-enhanced imaging (DCE), and proton magnetic resonance spectroscopy imaging (1H-MRS), may reflect the characteristics and physiological changes in the tumor microenvironment. DWI mainly describes the Brownian motion of water molecules, and provides information on tissue structure and cellularity. An isotropic apparent diffusion coefficient (ADC) obtained from DWI has been used as a quantitative parameter for differentiating malignant from benign lesions and monitoring treatment response [18]. By providing noninvasive morphologic and functional information on the tumor microvasculature, DCE-MRI can be useful for discriminating malignancies from benign lesions and monitoring treatment response in head and neck malignancies [19]. 1H-MRS is a powerful tool that can detect changes in biological compounds within tumors, and can be used for providing tumor-associated metabolic information [20]. Yet, none of these methods have been reported in the evaluation of SNPGLs. Therefore, the present study was aimed at exploring the value of multi-parametric functional MRI in the diagnosis of SNPGLs.

2. METHODS

2.1 Patients

This retrospective study was approved by the institutional review board of our hospital (no: 2014007). Four patients with pathologically confirmed SNPGLs were enrolled. All the patients underwent surgery in our hospital. In patient 3, paragangliomas occurred in the left nasal cavity 2 years ago, and was resected with no preoperative CT or MRI. Two years later, paragangliomas was found in the right nasal cavity, for which preoperative CT and MRI were available. In this study, we reviewed the images in the right nasal cavity. Patient 4 was defined as type III. Previous studies reported that because of the stability of Cr content, quantitative concentration of other compounds was normalized to Cr (N-acetylaspartate/Cr, creatine (Cr), choline (Cho), a combination of glutamine and glutamate, and inostitol, as previous studies reported. Because of the stability of Cr content, quantitative concentration of other compounds was normalized to Cr (N-acetylaspartate/Cr, Cho/Cr, and inostitol/Cr). We also observed whether peaks at other chemical shift positions were present.

2.2 Imaging techniques

CT was performed in all four patients. DWI was performed in patient 1, patient 2, and patient 3. DCE was performed in patient 1 and patient 2. 1H-MRS was performed in patient 1 and patient 2; and 1H-MRS was available in patient 1. The DWI parameters were as follows: TR/TE=3600/65 ms, number of average=1, b value=0 and 1000 s/mm². The DCE-MRI parameters were as follows: TR/TE=7.52 ms/2.06 ms, flip angle=15°, excitation number=1, field of view=220 mm, slice thickness=5 mm, temporal resolution=7 s/dynamic, number of dynamics=30. After the acquisition of two baseline scans, DCE-MRI was performed after intravenous administration of 0.1 mmol/kg gadopentetate dimeglumine (Magnevist, Bayer Schering, Berlin, Germany) at a rate of 3 mL/s, followed by 20 mL of a 0.9% saline flush. Multi-voxel 1H-MRS scanning was performed with PRESS with the following parameters: TR=1700 ms, TE=30 ms, averages=3, duration=6 min 53 s, VOI=30 mm×30 mm×5 mm, and voxel size=3.8×3.8×5 mm³. The FWHM was made as low as possible, first by automatic shimming and then manual shimming.

2.3 Imaging analysis

The raw DWI, DCE, and 1H-MRS data were processed offline on a Siemens workstation. An ADC map was generated through DWI images, and the slice presenting the largest diameter of the lesion was taken for measurement of values. Three regions of interest (ROIs) were manually placed within the lesions, and the average ADC value was calculated. ROIs were agreed upon by consensus, and care was taken to avoid necrosis, as well as adjacent arteries and veins. For DCE, an appropriate artery was semi-automatically selected to characterize the input function curve and concentration-time curve for setting the arterial input function. The signal intensity of the ROI was calculated to obtain the time-signal intensity curve pattern. A straight or curved line followed by a continuous signal increase was defined as type I; a relatively prominent increase slope with a plateau was defined as type II; and a fast initial signal increase followed by a signal decrease to a level lower than 90% of the peak grade was defined as type III.

For 1H-MRS, broad and intense overlapping peaks derived from fatty acids in the chemical shift range of 2.0 to 4.0 ppm were determined with the spectroscopy toolkit, including N-acetylaspartate, creatine (Cr), choline (Cho), a combination of glutamine and glutamate, and inostitol, as previous studies reported. Because of the stability of Cr content, quantitative concentration of other compounds was normalized to Cr (N-acetylaspartate/Cr, Cho/Cr, and inostitol/Cr). We also observed whether peaks at other chemical shift positions were present.

3. RESULTS

The clinical characteristics of the four patients are listed in Table 1. Nasal endoscopy showed that all four patients had nasal neoplasms, which were red or dark red, and the tumor surfaces were smooth. The clinical
presentation of the SNPGLs was atypical, and the common symptoms included repeated epistaxis, nasal obstruction, and rhinorrhea. Some patients also showed hypopharyngitis if the olfactory cleft was invaded. Patient 2 had left facial numbness and diminution of vision for more than 3 years, and the symptoms worsened as the disease progressed. CT and MRI showed that the tumor in patient 2 was mainly located in the left nasal cavity, pterygopalatine fossa, and middle skull base; the left inferior orbital fissure, orbital apex, cavernous sinus, infratemporal fossa were also invaded. Because no trigeminal nerve and optic nerve involvement was observed, patient 2 had symptoms of left facial numbness and impaired vision in the left eye. Additionally, patient 2 had high blood pressure, and hormone examination revealed elevated norepinephrine in the blood and urine, as well as dopamine in the urine, thus the paraganglioma was hormone-producing.

Histopathology is considered the gold standard for the diagnosis of paraganglioma. All cases were confirmed by histopathology in our study. The tumor cells were arranged in nested (Figure 1h), disperse (Figure 2g), or pseudo-alveolar (Figure 3d) architecture. The tumors contained two types of cells: chief cells and Sertoli cells. The chief cells composed the majority and were surrounded by the Sertoli cells. Immunohistochemical evaluation indicated that the chief cells had positive expression of synaptophysin and CD56 (Figure 3e, 3f), and negative expression of S-100 (Figure 3g), whereas the Sertoli cells had strong expression of S-100 (Figure 3g). Immunohistochemical staining for CD34 (Figures 1i, 2h) revealed that the tumors had abundant blood vessels.

All four patients had enhanced CT examination of the nasal cavity and sinuses, and three patients had enhanced MRI examination. Table 2 summarizes the CT and conventional MRI manifestations of the lesions. The maximum diameters of the tumors ranged from 1 to 5 cm. All patients had homogeneous iso-dense masses on unenhanced CT, and the lesions showed heterogeneous intense enhancement on postcontrast CT. The lesions showed heterogeneous isointensity in T1 weighted images and heterogeneous hyperintensity in T2 weighted images. All lesions had heterogeneous intense enhancement on postcontrast MRI. The margins

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Clinical Presentation</th>
<th>Duration of Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>Female</td>
<td>Right nasal obstruction</td>
<td>6 M</td>
<td>Surgery</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>Male</td>
<td>Left facial numbness, impaired vision</td>
<td>42 M</td>
<td>Surgery</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>Male</td>
<td>Rhinorrhea</td>
<td>4 M</td>
<td>Surgery</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>Female</td>
<td>Recurrent epistaxis</td>
<td>1 M</td>
<td>Surgery</td>
</tr>
</tbody>
</table>

M, months.

Table 1 | Clinical features of the four patients with sinonasal paragangliomas.

Figure 1 | A 66-year-old woman with SNP (patient 1).
The contrast-enhanced CT (a), T1WI MRI (c) and T2WI MRI (d) reveal a mass involving the right nasal cavity, the lateral ethmoid sinus, and sphenoid sinus. Unenhanced CT of the bone windows (b) shows the local bone absorption and destruction. The mass shows a relatively high signal on the ADC map (e), and the mean ADC value in the solid portion is 1.2×10⁻³ mm²/s. The mass has a type II time-signal pattern on DCE (f). ¹H-MRS (g) shows a high peak of choline and the presence of a succinate peak. The tumor cells are arranged in the nested architecture (h, HE ×10). Immunohistochemical staining of CD34 reveals a rich vascular network surrounding the tumor structure (i, ×10). Cho, choline; Cr, creatine; Suc, succinate.
of the lesions were well-defined in patients 1, 3, and 4, and ill-defined in patient 2. Moreover, extensive bone destruction was found in patient 2, thus potentially indicating relatively high tumor malignancy.

All tumors showed relatively high ADC values in the solid portions of the masses (Figures 1e, 2e, 3c). The mean ADC value in the solid portion was $1.2 \times 10^{-3}$ mm$^2$/s for patient 1, $1.1 \times 10^{-3}$ mm$^2$/s for patient 2, and $1.4 \times 10^{-3}$ mm$^2$/s for patient 3 (Table 3). DCE was available in patient 1 and patient 2, and indicated a type II pattern and type III pattern, respectively (Figures 1g, 2f). $^1$H-MRS spectra were acquired in patient 1. The Cho/Cr ratio was 12.9, and another peak of the compound succinate was detected at 2.4 ppm (Figure 1f).
4. DISCUSSION

Clinically, SNPGLs can be divided into two types: functional or non-functional, i.e., hormonally active with excess catecholamine secretion or hormonally silent, respectively [3]. Because of the hyper-vascular nature of functional SNPGLs, biopsy can result in substantial bleeding and might precipitate malignant hypertension [3, 4]. Therefore, non-invasive CT and MRI are crucial in preoperative diagnosis of SNPGLs. In this study, we analyzed multi-parametric functional MR imaging, including DWI, DCE, and 1H-MRS of three histologically demonstrated SNPGLs; the tumor microenvironment was explored through obtaining ADC values through DWI; the time-signal intensity curve pattern was determined through DCE; and metabolic changes were determined through 1H-MRS.

By detecting the movement of water molecules, DWI noninvasively reflects water diffusivity in tumors, which can be quantified by ADC values [21]. Previous studies have demonstrated that high cellularity of tumoral cells and high extracellular space tortuosity of tumor tissue usually pose large diffusion barriers to the movement of water molecules, thus leading to low ADC values [22]. In the sinonasal cavity, the ADC values of malignancies are usually reported to be lower than 1.0×10⁻³ mm²/s [21]. Yet, in our study, ADC values higher than 1.0×10⁻³ mm²/s were detected in all SNPGLs. This finding may be associated with the histological appearance of SNPGLs. Histologically, SNPGLs are characterized by nested zellballen structures surrounded by a fine vascular network [13]. Chief cells of the tumoral masses in SNPGLs were arranged in a zellballen pattern, which was nested and loose, with large extracellular spaces. Additionally, an abundant vascular network is usually present in SNPGLs, and water molecules move more freely in fast-flow vessels than in the solid portion of the tumor. Therefore, although SNPGLs have been suggested to be malignant, the ADC values of SNPGLs might be higher than those of other sinonasal malignancies, thus adding in the diagnosis of SNPGLs.

DCE-MRI mainly evaluates the microvascular blood flow, capillary permeability, and microvessel density, thereby providing a noninvasive macroscopic assessment of microvessel perfusion and neoangiogenesis. This method has also been used for tumor detection and characterization [19]. A previous study has reported that head and neck paraganglioma demonstrates a washout pattern on DCE [23]. In agreement with that finding, SNPGL demonstrated a type III pattern in patient 2 in our study, possibly because of the presence of bulky and plentiful feeding arteries within paragangliomas [3] and a rapid increase in signal intensity on DCE at the outset, constituting the ascending part of the curve. Furthermore, rapidly draining veins [3, 24-26] enabled the contrast agent to flow out quickly. Consequently, the signal intensity decreased and constituted the descending part of the curve. This result differed from the presentation of the type I pattern of benign sinonasal lesions.

Table 2 | CT and MRI findings of the four patients with sinonasal paragangliomas.

<table>
<thead>
<tr>
<th>Imaging Characteristic</th>
<th>No. 1</th>
<th>No. 2</th>
<th>No. 3</th>
<th>No. 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Right nasal cavity</td>
<td>Left nasal cavity, middle skull base</td>
<td>Right nasal cavity</td>
<td>Left nasal cavity</td>
</tr>
<tr>
<td>Margin</td>
<td>Well-defined</td>
<td>Ill-defined</td>
<td>Well-defined</td>
<td>Well-defined</td>
</tr>
<tr>
<td>Destruction of adjacent bone</td>
<td>Yes</td>
<td>Extensive bone destruction</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Signal intensity on MRI</td>
<td>Heterogeneous, isointense on T1WI, hyperintense on T2WI</td>
<td>Heterogeneous, isointense on T1WI, hyperintense on T2WI</td>
<td>Heterogeneous, isointense on T1WI, hyperintense on T2WI</td>
<td>NA</td>
</tr>
<tr>
<td>Enhancement on postcontrast CT/MRI</td>
<td>Heterogeneous, intense</td>
<td>Heterogeneous, intense</td>
<td>Heterogeneous, intense</td>
<td>Heterogeneous, intense</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

NA, not available.

Table 3 | DWI, DCE, and 1H-MRS of three of the patients with sinonasal paragangliomas.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>ADC Values (mm² s⁻¹)</th>
<th>Time-signal intensity curve pattern</th>
<th>Highest Cho/Cr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2×10⁻³</td>
<td>Type II</td>
<td>12.9</td>
</tr>
<tr>
<td>2</td>
<td>1.1×10⁻³</td>
<td>Type III</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>1.4×10⁻³</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
Original Research

thus potentially aiding in differentiating malignant from benign tumors. Yet, our study also showed a type II pattern of SNPGLs in patient 1. We speculated that the plateau of the curve suggested that draining veins were limited in some SNPGLs. Immunohistochemical staining of CD34 (Figures 1i, 2h) revealed that the tumors had abundant blood vessels. Hence, DCE-MRI may be used to assess the abundant microvessel perfusion and neoangiogenesis in SNPGLs.

$^1$H-MRS is a tool with potential to relate cellular and molecular biochemistry to tumoral pathology by providing metabolic information. It enables the analysis of specific metabolites semi-quantitatively and the non-invasive detection of peaks of specific compounds, thus facilitating the diagnosis of head and neck diseases [27]. In the current study, the succinate peak was detected at 2.44 ppm, thereby indicating abnormality of the succinate metabolite in SNPGLs. This result may be explained by paragangliomas being associated with a mutated succinate dehydrogenase gene, thus resulting in succinate dehydrogenase enzyme deficiency [28, 29]. Without the succinate dehydrogenase enzyme, the oxidation of succinate to fumarate in the Krebs cycle is blocked [30], thus causing accumulation of succinate [31]. This study provides the first report of the succinate peak in SNPGLs. Our findings may greatly aid in the differentiation of SNPGLs from other sinonasal neoplasms. Furthermore, the ratio of Cho/Cr in SNPGLs was found to be 12.9, higher than the value of <5 reported in benign sinonasal lesions [32, 33]. This difference might have been due to the numerous membrane-round granules of the chief cells [3], and increased cell proliferation and membrane biosynthesis in SNPGLs. Hence, the characteristic succinate peak and a high ratio of Cho/Cr might further facilitate the diagnosis of SNPGLs.

Because SNPGLs are rare, the main limitation of this study was its small sample size. Therefore, more cases will be needed for further investigations in the future. Additionally, owing to the retrospective nature of this study, DWI, DCE, and $^1$H-MRS were not performed in all patients. In the future, we will continue to investigate the functional MRI of SNPGLs.

In conclusion, imaging features of SNPGLs, were studied through functional MRI, included an ADC value higher than $1.0 \times 10^{-3}$ mm$^2$/s from DWI, a type III or type II pattern from DCE, and a high Cho/Cr ratio and a characteristic succinate peak from $^1$H-MRS. These characteristics reflect the pathological microenvironment within the tumoral mass and may aid in the differentiation of SNPGLs from other sinonasal neoplasms.

CONFLICTS OF INTEREST

None.

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REFERENCES


The characteristic succinate peak and high ratio of Cho/Cr might further help in the diagnosis of SNPGLs.

- Although sinonasal paragangliomas (SNPGLs) have been suggested to be malignant, the apparent diffusion coefficient (ADC) values of SNPGLs might be higher than those of other sinonasal malignancies.

- Dynamic contrast-enhanced imaging (DCE)-MRI may assess the abundant microvessel perfusion and neoangiogenesis in SNPGLs.

- The characteristic succinate peak and high ratio of Cho/Cr might further help in the diagnosis of SNPGLs.