Perineural spread along trigeminal nerve: a review of cases

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Learning objectives

To learn the anatomy of trigeminal nerve (CNV).

To review definition and pathogenesis of perineural spread (PNS)

To assess the proper technique and typical findings
Background

Perineural Spread (PNS) is a way of tumor dissemination along the tissue of the nerve sheath, associated with different types of head and neck tumors.

It is important to recognize this entity because it has a detrimental influence on the prognosis and it requires more extensive surgical resections and wider radiation fields for complete control tumor.

The main pathways for PNS are cranial nerves, especially CNV, because it has greater regional extension and is close to the anatomical areas of the tumors that most often present PNS.

Perineural spread has a wide variety of clinical manifestations. Patients can experience pain, burning, or dysesthetic sensations along the path of the involved nerve. With advanced disease, complete denervation can lead to muscle atrophy. However, up to 45% of patients with radiographic or histological perineural invasion are completely asymptomatic.

Diagnose PNS can be very challenging due to the fact that not all patients report clinical signs of perineural spread. The anatomy in the head and neck region of cranial nerves is very complex and radiological signs can be very subtle.

Finally, there are certain histological types of tumors which are especially prone to perineural spread. These are: epidermoid carcinomas, adenoid cystic carcinomas and melanomas. Also certain locations are prone to perineural spread: nasopharynx, parotid and sublingual glands and deep skin tumors.
Findings and procedure details

To understand and define patterns of PNS it must be known the anatomy of the CNV. (Fig.1 and Fig.2)

Trigeminal nerve:

The trigeminal nerve is a mixed nerve (both sensory and motor components) and has four segments: Intra-axial, cisternal, interdural and extracranial. Although the spread can reach all segments, interdural and extracranial are more often affected.

It has four nuclei (3 sensory, 1 motor) located in the brainstem and upper cervical cord, and leaves the pons in a rather lateral position. It courses straight through the pre-pontine cistern to enter through the Meckel's Cave into the Gasserian ganglion. There, the ophthalmic, maxillary, and mandibular branches of the trigeminal nerve leave the skull through 3 separate foramina: the superior orbital fissure, the foramen rotundum, and the foramen ovale, respectively.

Ophthalmic nerve V1

The ophthalmic nerve is the first branch of the trigeminal nerve. It arises from the convex surface of the Gasserian ganglion, in the dura of the lateral wall of the cavernous venous sinus under CN IV and above the maxillary nerve.

Just before it exits the skull through the superior orbital fissure, it gives off a dural branch, and then divides into 3 branches: the frontal, lacrimal, and nasociliary.

Maxillary nerve V2

The maxillary nerve is divided into 3 branches: the zygomatic, sphenopalatine (or pterygopalatine), and posterior superior alveolar nerves.

As it leaves the Gasserian ganglion, the maxillary nerve passes through the dura of the lateral wall of the cavernous sinus. It exits the skull via the foramen rotundum and crosses the pterygopalatine fossa (important location of perineural spread) to enter the orbit through the inferior orbital fissure, where it becomes the infraorbital nerve.
The zygomatic, sphenopalatine and posterior superior alveolar branches are given off in the pterygopalatine fossa.

In the lateral wall of the orbit, it gives off a branch to the lacrimal nerve, which carries postganglionic fibers from the sphenopalatine ganglion for lacrimation. The zygomaticofacial is located in the lower part and supplies the skin of the cheek.

The sphenopalatine (or pterygopalatine) nerve are in fact 2 nerves that unite the sphenopalatine ganglion to the maxillary nerve. They transmit afferent sensations from the nose, palate, and pharynx. They also carry parasympathetic fibers to the lacrimal nerve that go to the lacrimal gland. These preganglionic fibers are derived from CN VII via the greater petrosal and vidian nerves.

**Mandibular Nerve (V3) (2):**

The mandibular nerve runs laterally along the skull base then exits the cranium by descending through the foramen ovale into the masticator space. It divides into two trunks: The anterior trunk or motor trunk to innervate masticator muscles and the posterior trunk that is mainly sensorial nerve.

Auriculotemporal nerve - it emerges superficially between the ear and the mandibular condyle, deep into the parotid gland and ends in 2 superficial temporal branches

Lingual nerve - This nerve runs parallel to the inferior alveolar nerve, is joined by the chorda tympani nerve of the facial nerve (CN VII)

Inferior alveolar nerve - This nerve accompanies the inferior alveolar artery in the mandibular foramen and enters into the mandibular canal to exit through the mental foramen.

**ZONAL CLASSIFICATION**

The zonal classification allows us to describe the anatomical extent of perineural spread view in RM. This system determines the surgery, subcranial vs. resection of skull base (19) and has proven to be a predictor of overall survival (43).
Three zones have been described, whose limits are defined by the affected cranial nerve (V or VII) and the different branches of the V cranial nerve (V1, V2 or V3) (Table 1).

<table>
<thead>
<tr>
<th>Zone 1</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
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<tr>
<td></td>
<td>to the superior orbital fissure</td>
<td>to the external aperture of the</td>
<td>to the external aperture of the</td>
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<tr>
<td></td>
<td></td>
<td>foramen rotundum</td>
<td>foramen ovale</td>
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<tr>
<td>Zone 2</td>
<td>From zone 1 to the Gasserian ganglion cistern</td>
<td></td>
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<tr>
<td>Zone 3</td>
<td>Encompasses all nerves from the Gasser ganglion into the cisterns or into the brainstem</td>
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**CLINIC**

Up to 45% of patients with PNS are asymptomatic even with extensive involvement. On the other hand, there are patients with suggestive clinical data of PNS without findings on imaging studies (4, 5).

In general, clinical involvement is belated, subtle and nonspecific. (6). It should be suspected when there is insidious involvement of cranial nerves, slowly progressive, or when we find a unilateral involvement of multiple cranial nerves (Garcin syndrome) (6).

**IMAGING TECHNIQUES**

Imaging techniques used in the diagnosis of this entity are MRI, CT and PET-CT. The MR is the choice for the contrast resolution. However, although its use is not yet widespread, there are reports in the recent literature about the new PET-MRI that suggest it could have even greater accuracy in the diagnosis of this entity (7).

**MR**

We recommend the use of isotropic volumetric sequences with high spatial resolution T1-weighted (8). These can be applied with or without fat saturation. Fat saturation techniques allow us to delineate enhancing lesions that are close to spaces that
contain fat, as the orbits, the pterygopalatine fissure and neurovascular foramina. These sequences are chosen by most radiologists (12,11). However, some authors prefer sequences without fat saturation ("fat is a friend") (9,10) because they allow to see clearly the fatty packages adjacent to foramina and because, even after gadolinium, the tumor will never have the same hyperintensity as the fat ("evil gray"). Also, without fat saturation, we avoid the susceptibility artifacts frequently observed in sequences with saturation.

The protocol in our center consists of T1-weighted sequences without fat saturation before contrast administration and then T1-weighted sequences with fat saturation after administration of gadolinium.

T2-weighted sequences are necessary when zone 3 is involved, for the study of cisternal and intraaxial path cranial nerves. Furthermore, the additional use of fat saturation may be useful to assess the inflammatory component associated with this entity, especially in locations where nerves are related to fatty packages.

CT

CT assesses very well the morphology and size of the bony foramina and skull base canals. PNS is associated with expansion and enlargement of foramina and it is not frequent aggressive pattern like mottle or permeative.

PET-CT

PET-CT is useful in the study of head and neck cancers mainly because it has proven to be superior to CT and MRI in the evaluation of lymph node and detection of residual and recurrent tumors (13). However there is not concluding data on its sensitivity and specificity in detecting PNS. Nevertheless the existence of any linear or curvilinear focus of abnormal FDG uptake in the anatomical distribution territories of the cranial nerve is sufficient to suspect the existence of PNS and correlate the findings with data from MRI to confirm the diagnosis (14).

IMAGING FINDINGS:

PRIMARY FINDINGS

The primary findings are related to the direct affectation of the nerve by the tumor. We can distinguish:
**Full enhancement** of the entire circumference of nerve in T1-weighted gadolinium enhanced sequences (due to the breaking of the hematoneural barrier) and a **thickening** of the normal nerve (11,15). Full enhancement of the pathological nerve should be differentiated from the symmetrical peripheral enhancement and variable thickness of a normal nerve (target appearance). This peripheral enhancement is secondary to the perineural venous plexus and is seen frequently in the foraminal segments of the three branches of the trigeminal nerve and in the geniculate ganglion.

- **Loss of the perineural fat pad** within foramina containing a cranial nerve branch. It occurs as a result of tumor growth and its inflammatory component.

- **Enlargement of the foramina.**

- **Spreading to the intracranial compartment.** It is associated with infiltration of the cavernous sinus, bulging of the lateral wall, adjacent dural thickening of the affected nerve segments and thickening and/or enhancement of the cisternal and fascicularis segments of affected cranial nerves

**SECONDARY FINDING:**

As a result of the neural affectation it appears **denervation atrophy**. This finding is most frequent in mastication muscles (by involvement of V3 CN) and tongue (by affecting the hypoglossal muscle) and less common in the muscles of facial expression (16).

A series of images is presented, showing the various zones of perineural spread of the branches of the trigeminal nerve (Fig. 3 to 12).

**CONSIDERATIONS**

In addition to the findings described above three considerations should be taken into account:

- The findings of PNS may persist indefinitely despite clinical improvement. Therefore recurrence should be suspected when there is growth of the lesion on the image or clinical worsening (10).

- When making the staging of malignant tumors of the head and neck, especially those associated with an increased incidence of PNS, the route of all cranial nerves should
be exhaustively studied. Due to the extensive network of connections any nerve may be potentially affected.

- The affectation of a nerve may seem discontinuous in the image even if exists continuous histological involvement (19.57). It is called "skip metastases" (17,18). This radiologic-histology discrepancy is due to the fact that there are segments of the nerve where the tumor is so small that may not be visible on imaging studies (20).
**Fig. 1:** Anatomy of the trigeminal nerve

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Fig. 2: Anatomy of the trigeminal nerve

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**Fig. 3:** 3 Axial T1 post gadolinium. Squamous cell carcinoma of the face spreading to the V1 in the cavernous venous sinus and infiltration the midbrain.

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**Fig. 4:** CT coronal bone window. The orbital roof (frontal bone) shows focal areas of thinning with bony erosion due to PNS of a Squamous cell carcinoma of the face along V1 CN.

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**Fig. 5:** Coronal T1-weighted post-contrast MR. Note asymmetrical enhancing soft tissue in the left cavernous sinus due to infiltration of V1 of a squamous cell carcinoma of the face along V1 CN.

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**Fig. 6:** Axial T1 post gadolinium. Perineural spread of a melanoma in the nose through V2. Infiltration of left Meckel’s cave and midbrain, as well as thickening and enhancement of the cisternal segment of trigeminal nerve.

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Fig. 7: Coronal T2-weighted image shows clear erosion and enlargement of the infraorbital canal. Perineural spread of malignant melanoma was confirmed.

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Fig. 8: Sagittal T1-weighted post gadolinium image. It is shown PNS along V1 and V2 skull base and peripheral segments. Also you clearly depict implication of cisternal segment of V CN secondary to adenoid cyst carcinoma

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**Fig. 9:** Axial T2-weighted image shows clear enlargement of the left infraorbital canal. Perineural spread of malignant melanoma was confirmed.

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Fig. 10: Axial T1 post gadolinium. Perineural spread along V3 CN into foramen ovale and cavernous sinus involvement. This patient had a nasopharynx cancer.

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Fig. 11: PNS along left greater petrosal superficial nerve and vidian nerve due to adenoid cystic carcinoma of maxillary sinus

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**Fig. 12:** 12: CT coronal bone window. Clear enlargement of the left foramen oval. This finding was secondary to PNS along V3 CN in a nasopharynx cancer.

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Conclusion

Perineural spread is a form of metastasis which occurs more frequently in tumors of the head and neck. It often passes unnoticed in imaging studies, and yet, their presence modifies treatment protocols, is associated with a higher rate of local recurrence and is considered an independent prognostic factor in the TNM classification of malignant tumors.

Certain tumor strains are associated with a higher prevalence of PNS. It is essential the knowledge of this association and the anatomy of cranial nerves, specially CN V, and its rich neural connections. MRI, with its higher resolution and multiplanar capability, allows to study the neural path from the peripheral region to the core region, and to discard the increase of thickness, enhancements, and complete obliteration of fat planes that are characteristic primary findings of this type of tumor spread.
References


