

Paragangliomas

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Paragangliomas - **neoplasms derived from PARAGANGLIA**.

Paraganglia (s. chromaffin bodies) – small (< 1.5 mm) roundish bodies, function as **chemoreceptors** in *diffuse neuroendocrine system* (formerly called *APUD*):

- 1) **glomus intravagale** – minute collection of chemoreceptor cells on auricular branch of vagus nerve, in proximity to ganglion vagale inferior (nodosum).
- 2) **glomus jugulare** – minute collection of chemoreceptor cells in adventitia of jugular bulb (within jugular foramen of temporal bone).
- 3) **glomus tympanicum** – on tympanic (Jacobson) nerve (on promontory of middle ear).
- 4) **carotid body (s. glomus caroticum)** – chemoreceptor (O₂, CO₂, H⁺) innervated by CN9.
- 5) **glomus pulmonale** – structure similar to carotid body, found in relation to pulmonary artery.
- 6) **paraortic bodies (s. glomera aortica, organs of Zuckerkindl)** – chemoreceptors (O₂, CO₂, H⁺) innervated by CN10.
- 7) **coccygeal body (s. glomus coccygeum) ?**

Term “glomus” mistakenly was attached to these organs when their origin was believed to be similar to true glomus (arteriovenous) complexes, and although now recognized as inaccurate, nomenclature has persisted.

- paraganglia derive from neural crest in close association with autonomic nervous system.
- paraganglia are composed of clusters of **epithelioid (chief) chromaffin cells**.

PHEOCHROMOCYTOMA – paraganglioma of adrenal medulla.

CHEMODECTOMA – nonchromaffin paraganglioma; i.e. tumor of chemoreceptors in paraganglia (tumor does not include chromaffin cells).

GLOMUS JUGULARE TUMOR, GLOMUS TYMPANICUM TUMOR

- **benign, slow-growing but locally invasive, encapsulated, highly vascular tumor of chief cells of glomus jugulare / tympanicum** (i.e. nonchromaffin paraganglioma, s. chemodectoma).

- rare - INCIDENCE is 1 case per 1.3 million people.
- **most common tumor of middle ear** (second to *VESTIBULAR SCHWANNOMA* as most common tumor of temporal bone).
- predominantly **women** (3-6 : 1) 40-70 years (6 months – 88 years).
- most are **sporadic**.
- rarely - **familial** with autosomal dominant inheritance and incomplete penetrance; genomic imprinting - only children of males possessing disease gene (11q23) develop tumors.

PATHOLOGY

- **histology** - resembles normal paraganglia - clusters of chief cells (termed “zellballen” = Germ. “cell balls”) in highly vascular stroma; pattern is enhanced on silver staining (useful diagnostically); sustentacular cells and axons, seen in normal paraganglion, rarely appear in tumor.
- **macro** - reddish purple vascular lobulated mass.
- more common on left side.
- **multicentric** in 3-10% sporadic cases and in 25-50% familial cases.
- expands within temporal bone via pathways of least resistance (air cells, sigmoid and inferior petrosal sinuses, skull base foramina, eustachian tube); tumor tends to obstruct internal jugular vein.
- also **erodes bone** in lobular fashion (but often spares ossicular chain) - region of jugular fossa and posteroinferior petrous bone → mastoid and adjacent occipital bone.
Significant intracranial and extracranial extension may occur!
- 4% cases **metastasize** (lung, lymph nodes, liver, vertebrae, ribs, spleen).
- 1-4% tumors produce clinically significant levels of catecholamines (**norepinephrine** or **dopamine**) - mimicking *PHEOCHROMOCYTOMA*.

FISCH classification (tumor extension to surrounding structures):

- Type A tumor - limited to middle ear cleft (glomus tympanicum)
- Type B tumor - limited to tympanomastoid area with no infralabyrinthine compartment involvement
- Type C tumor - involving infralabyrinthine compartment of temporal bone and extending into petrous apex
- Type C1 tumor - limited involvement of vertical portion of carotid canal
- Type C2 tumor - invading vertical portion of carotid canal
- Type C3 tumor - invasion of horizontal portion of carotid canal
- Type D1 tumor - intracranial extension < 2 cm in diameter
- Type D2 tumor - intracranial extension > 2 cm in diameter

CLINICAL FEATURES

- insidious onset (significant delay in diagnosis):

- 1) loud pulsatile **tinnitus** (76%; tumor is vascular!) + **earache** – features differentiating from *VESTIBULAR SCHWANNOMA*!
Significant ear pain is uncommon!
- 2) **conductive hearing loss** (52%; inhibited ossicular mobility).
- 3) **middle ear mass, ear fullness** (18%), **bruit**; erosion laterally **through drum** → **otorrhea, external canal bleeding** (7%) - mimics friable bleeding polyp.
- 4) erosion laterally to **inner ear** → **sensorineural hearing loss** (5%), **vertigo** (9%), **CN7 palsy**.
- 5) pathognomonic for glomus jugulare tumor - **jugular foramen syndrome** (CN9-11 paresis; nerves are situated medial to jugular bulb); lags ≈ 1 year after initial symptoms.
- 6) in 1-4% cases, leading symptoms are **pheochromocytoma-like** (hypertension, tachycardia); also, **somatostatin, VIP, calcitonin, neuron-specific enolase** may be produced by tumor (**carcinoid-like** symptoms).
- 7) **intracranial** extension → cerebellar / brainstem symptoms, dural sinus involvement, hydrocephalus, ICP↑.

DIAGNOSIS

Otoscopy - characteristic, pulsatile, reddish-blue tumor behind tympanic membrane (tip of iceberg).
BROWN sign - pulsatile purple-red middle ear mass that blanches with positive pneumatic otoscopy - distinguishing sign (often of little clinical value).

Audiology - mixed conductive and sensorineural hearing loss.

Plain X-ray - enlargement of lateral jugular foramen and fossa.

CT with thin sections - extent of bone destruction.

Contrast MRI (reflects highly vascular nature) - characteristic soft tissue intensity intermixed with high-intensity signals and signal voids ("salt & pepper" appearance); bright enhancement.

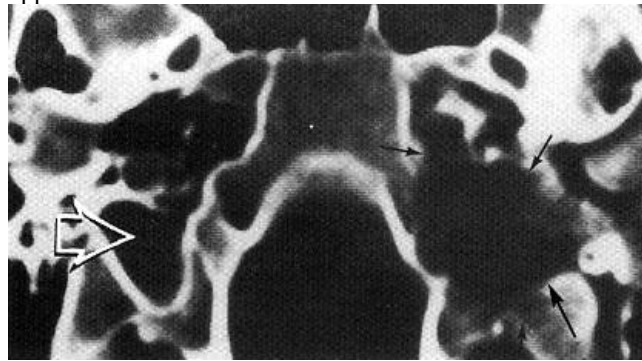
- some advocate that imaging be carried *down to carotid bifurcation* - to determine if multiple tumors exist.

Just before surgery (to allow embolization in one session) - carotid **arteriography** with cross-compression or trial balloon occlusion;

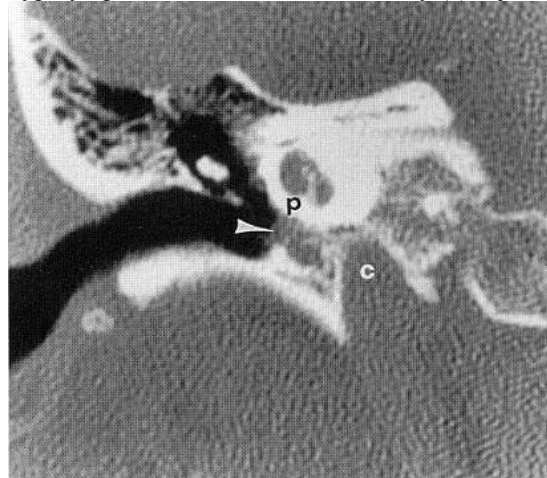
- **blood supply** is via ascending pharyngeal artery from ECA and branches from petrous portion of ICA.
- for tumors with large intracranial extension → vertebral arteriography (to exclude arterial feeders from posterior circulation).

Biopsy is likely to cause significant hemorrhage!

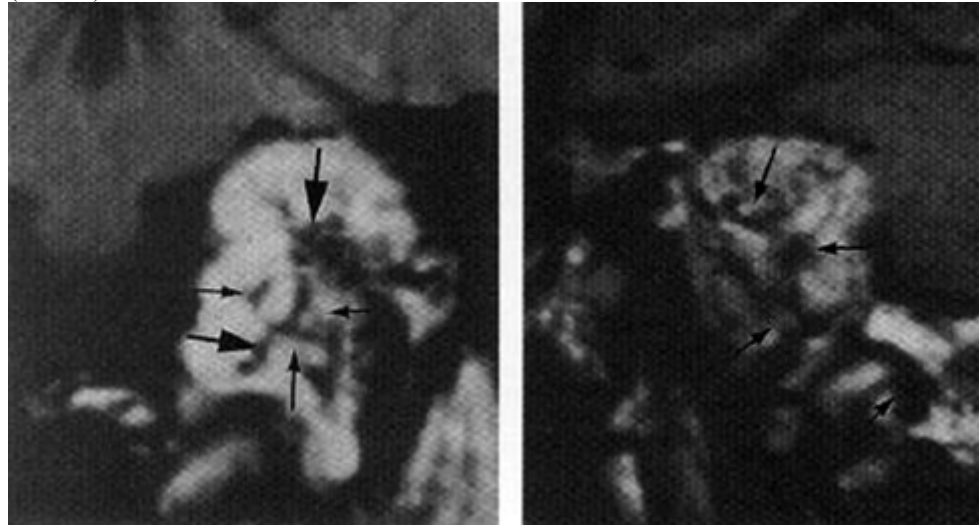
Glomus jugulare tumor (axial CT bone-window at foramen magnum level) - right jugular foramen (*open large arrow*) is smoothly rounded and densely corticated, but left is enlarged (*small black arrows*) and bone surrounding it appears 'moth-eaten':



Glomus tympanicum tumor (coronal CT) - soft-tissue mass (*arrowhead*) along cochlear promontory (p) and hypotympanum; note that carotid artery (c) is just inferomedial to mass:



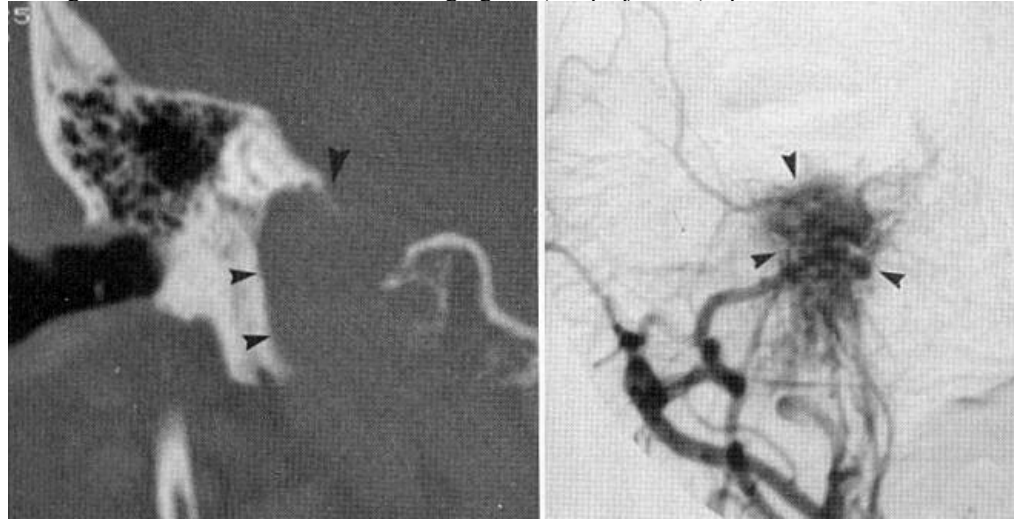
Glomus jugulare tumor (contrast T1-MRI) - marked enhancement with flow voids, representing large veins (*arrows*):



Glomus jugulare tumor:

A: Coronal CT - expansion of jugular fossa (*small arrowheads* indicate lateral wall) and destruction of petrous apex (*large arrowhead*).

B: Digital subtraction external carotid angiogram (AP projection) - pronounced tumor vascularity (*arrowheads*).

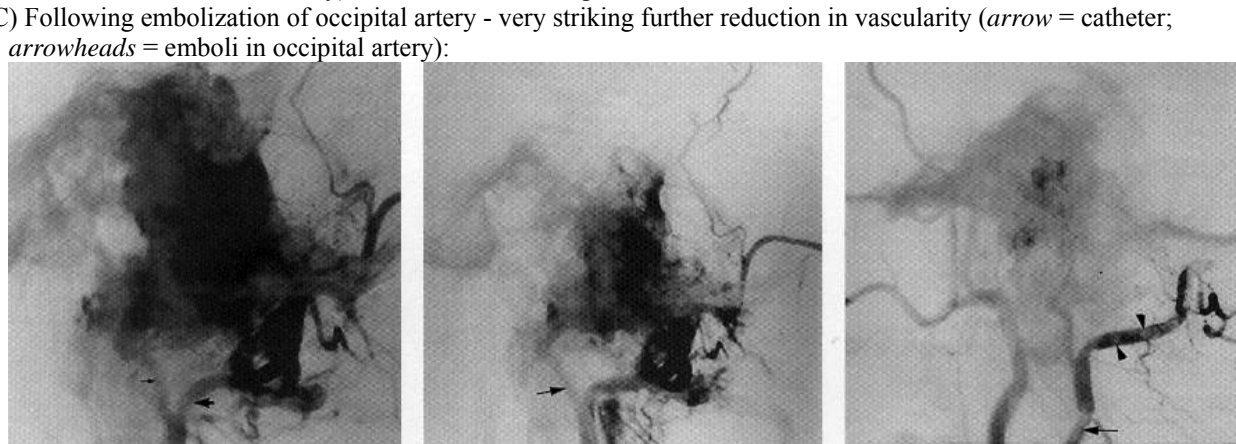


Glomus jugulare tumor (angiography):

A) Lateral projection, injection of occipital artery, arterial phase - large, extremely vascular mass fed by posterior auricular (*small arrow*) and occipital (*large arrow*) arteries.

B) Lateral projection after particulate embolization of anterior feeding vessel (posterior auricular artery) (*arrow* indicates catheter within artery) - bulk of mass no longer stains.

C) Following embolization of occipital artery - very striking further reduction in vascularity (*arrow* = catheter; *arrowheads* = emboli in occipital artery):



TREATMENT

Some cases require no treatment! (e.g. elderly patient with small tumor that grows slowly)

Drug therapy:

1. **α- and β-blockers** for tumors *secreting catecholamines** (esp. for 2-3 weeks before embolization and/or surgery - to avoid potentially lethal BP lability and arrhythmias).
 * ≥ 3 times reference range
2. **OCTREOTIDE** – for growth control of *somatostatin receptor-positive* tumors.
3. **ETOPOSIDE, CISPLATIN** – for **metastases**.

Surgery – treatment of choice!

- preoperative embolization (immediately after the diagnostic angiogram).
- routine intraoperative monitoring (EEGs, SSEPs).
- sigmoid sinus above and jugular vein below are ligated, and segment between them excised with attached tumor;
 - temporarily occlude transverse or sigmoid sinus (with EEG monitoring) to determine whether vein bypass should be performed for total resection.
- approach:
 - Fisch type A tumor** – transmeatal or perimeatal approach.
 - Fisch type B tumor** – extended posterior tympanotomy.
 - Fisch type C tumor** – standard combined transmastoid-infratemporal or transtemporal-infratemporal approach with or without ICA trapping, preceded by ECA or superselective embolization.
 - Large **Fisch type D tumor** – combined otologic and neurosurgical approach (infratemporal approach with skull base resection and posterior fossa exploration).
- partial resection → radiation.

Classic fractionated radiotherapy or **radiosurgery** – both are successful in long-term control of tumor growth (esp. with doses ≥ 40 Gy):

- a) adjuvant after subtotal resections.
 - b) sole treatment modality for symptomatic elderly / infirm patients with extensive or growing tumors.
- dose of 45 Gy in 5 weeks is recommended.
 - paragangliomas are *radiosensitive* but *not radiocurable!*

FOLLOW-UP, PROGNOSIS

Radiologic (\pm endocrinologic) monitoring for tumor growth / regrowth every 6 months for 2 years → every 2 years.

Survival at 20-yrs - 94% (77% are symptom free).

Prognosis is excellent!

BIBLIOGRAPHY for ch. “Neuro-Oncology” → follow this [LINK >>](#)