

TITLE: Cerebellopontine Angle Tumors with Focus on Vestibular Schwannomas

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Introduction

The cerebellopontine angle (CPA) is a dense area of vital neurologic tissue. Tumors growing in this region can cause significant dysfunction and even death if allowed to grow too large. They represent 10% of all intracranial tumors and although the differential is quite extensive, 78% of tumors in this region are vestibular schwannomas (1). The second and third most common tumors in this region are meningiomas and epidermoid tumors respectively. Autopsy studies have shown an incidence of CPA tumors to be 1.7 to 2.7% however a single MRI study looking at 10,000 films obtained for non-otologic reasons showed only 7 positive cases (2-4). Because of the significant dysfunction these tumors can cause, timely diagnosis and treatment are paramount.

History of CPA tumors

In 1894 Sir Charles Balance was the first surgeon to successfully remove a vestibular schwannoma. Due to the significant morbidity of the surgery, however, his first patient died shortly after the operation from complications. In 1907, Balance, improved upon his previous outcome and performed a successful surgical excision without the patient mortality. Despite this outcome the patient still had significant facial nerve paralysis complicating the excision (5,6). In 1917 Harvey Cushing pioneered the subtotal resection through bilateral suboccipital craniectomy and described the CPA syndrome (7). The CPA syndrome is the constellation and progression of symptoms as a CPA tumor grows larger. Cushing described it as ipsilateral hearing loss followed by facial hypesthesia, hydrocephalus, and finally brainstem compression and death.

Despite the high morbidity and mortality rates, surgeons continued to improve upon previous results, and in 1925 Walter Dandy reported a mortality rate of only 10% using a debulking and capsular resection technique (8). Most recently in the 1960's William House advanced the

surgical technique of resecting CPA tumors by introducing the microscope and dental drill, the translabyrinthine approach, and the middle cranial fossa approach (9-11). Much of what House accomplished is still considered standard of care today.

Anatomy and Tumor Biology

As stated previously, the CPA is an area densely packed with neurologic tissue and any tumor growth can cause significant dysfunction. Cranial nerves V-VIII are affected with more superiorly based tumors, whereas tumors that extend inferiorly can compress cranial nerves IX-XII. Extension to the cerebellum laterally can cause generalized ataxia and even optokinetic difficulties with compression on the flocculus. Brainstem compression leading to fourth ventricle obstruction can lead to hydrocephalus, respiratory depression, and death.

Vestibular Schwannomas arise from Schwann cells within the IAC and arise from the Schwann cell rich zone of Scarpa's ganglion (1). There is an equal frequency of vestibular nerve involvement between the superior and inferior segments, however involvement of the acoustic portion of the nerve is rare.

Vestibular schwannoma formation is thought to be due to a defect in the tumor suppressor gene NF2 found at 22q12. The NF 2 gene prevents Schwann cell proliferation. The sporadic form of unilateral vestibular schwannomas represents 95% of cases (12). In this case there are two hits to the normal NF gene. Patients with Neurofibromatosis 2, however, inherit one defective gene in an autosomal dominant manner, and then develop a genetic defect in the second normal allele. For this reason they are predisposed to developing bilateral vestibular schwannomas.

Several studies have looked at the biochemical effects of different agents on the growth of vestibular schwannomas. Neuregulin is a hormone expressed by Schwann cells to control proliferation and survival of Schwann cells (1). Several chemokines such as FGF, TGF-B, VEGF, and PDGF are all chemokines that have been evaluated as potential targets to prevent tumor growth (13-16). Studies in the past had previously shown increased growth of vestibular schwannomas during pregnancy but more recent studies have failed to show an increased growth rate dependent on sex hormones or their receptors (17).

Symptoms and Signs

Symptoms and signs are highly dependent on the epicenter of the tumor. Intracanalicular tumors often present with hearing loss, tinnitus, or vertigo. Tumors extending into the CPA will likely have disequilibrium or ataxia depending on the amount of extension on the brainstem. With Brainstem extension midface hypesthesia, hydrocephalus, and other cranial neuropathies become more prevalent. Vestibular schwannomas most commonly present with sensorineural hearing loss, followed by tinnitus, disequilibrium and facial hypesthesia in decreasing order (12).

Unilateral hearing loss is present in greater than 85% of patients (18) but 5% of patients with vestibular schwannoma will have no associated hearing loss (19). In most instances of retrocochlear losses, despite the sensorineural hearing loss, many patients will have speech discrimination scores proportionally worse than the observed hearing loss. Patients will therefore complain of difficulty when talking on the telephone.

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Sudden SNHL will be present in about 20% of patients with a vestibular schwannoma (12), but only 1% of patients with sudden SNHL have a vestibular schwannoma (20). Fifty percent of patients with vestibular schwannoma and sudden SNHL will have spontaneous recovery and therefore you cannot simply rule out a vestibular schwannoma if they recover.

Tinnitus is the second most common presenting symptom and can present in a variety of ways. It can be present without hearing loss, it can be described as a roar, a high pitch ring, or even hissing, and it can even localize to the opposite ear. Therefore any person with a complaint with unilateral hearing loss should at least be evaluated with an audiogram.

Vestibular complaints are present in 36-50% of patients and will describe a vague or transient lightheadedness. They often will just have some disequilibrium. Acute vertigo is the presenting symptom in only about 27% of patients and is associated with smaller tumors (1).

Facial hypesthesia is the presenting symptom in only 4% of patients, is associated with larger tumors >2cm and commonly will affect the maxillary division of cranial nerve V first. The corneal reflex is often the first symptom but involvement of the muscles of mastication can also occur. Facial weakness is rare with vestibular schwannomas, and if present, should be grounds to assume there is a different type of tumor.

Ocular complaints are rare and can range from simple loss of corneal reflex, to true ocular dysfunction. Nystagmus toward the affected side, diplopia from involvement of cranial nerve VI, and blurry vision from hydrocephalus leading to papilledema and optic atrophy.

Physical exam findings of an acoustic neuroma can include an absent corneal reflex, weakness of the temporalis or masseter muscles, hypesthesia to pinprick and touch, nystagmus, and other cranial neuropathies. Histelberger's sign is present when the sensory portion of cranial nerve seven is absent but the motor portion is intact. The actual sign is hypesthesia of the external canal (1). Finally you may identify gait disturbances or difficulties on finger to nose testing.

Workup

Audiologic testing is paramount when evaluating a patient with a suspected CPA tumor or vestibular schwannoma. A downsloping high frequency hearing loss is the most common finding on audiogram in about 65% of patients (21). Five percent of all patients will have no hearing loss (22). Rollover is a term used to represent retrocochlear hearing loss where patient's speech discrimination is worse than expected based on pure tone averages that become worse as the sound is intensified.

There are two classifications used to represent the different stages of hearing loss and can be seen in Table 1. Many papers use these classifications to compare preoperative and postoperative hearing abilities for qualitative purposes. Most papers recognize serviceable hearing as AAO-HNS class A or B and Gardner-Robinson class 1 or 2. Hearing classification is also very important when determining what surgical procedure a patient is qualified for based on their preoperative hearing scores.

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AAO-HNS classification		
Class	Pure tone average (0.5, 1, 2, 3 kHz measured in dB HL)	Speech discrimination score (%)
A	0-30	70-100
B	31-50	50-100
C	>50	50-100
D	Any	<50
Gardner-Robertson Classification		
Class	Pure Tone/Speech Reception Threshold (dB HL)	Speech Discrimination Score (%)
1	0-30	70-100
2	31-50	50-69
3	51-90	5-49
4	>90	1-4

Table 1. Showing different classification schema for hearing loss.

In addition to audiologic testing, acoustic reflexes can also be used to show a retrocochlear loss. Acoustic reflex testing has an 85% sensitivity for identifying abnormalities. An abnormal test will be an increased or absent acoustic reflex threshold compared to cochlear norms. This is not considered a reliable screening test.

Auditory Brainstem Evoked Response testing has a sensitivity of 85 to 90% with a false positive rate of only about 10%. False negative rates were much lower in the past but have increased to about 18-30% due to improvements of imaging techniques to find smaller tumors (24). During the test five waveforms are produced and a latency of >0.2 milliseconds in wave V is diagnostic of a retrocochlear loss. In patients with a low index of suspicion for a vestibular schwannoma, this test can be used for screening purposes.

Vestibular testing or electroneurography will show some form of abnormality in 70-90% of patients (25) but 50% of small tumors will produce no abnormalities (26). Abnormalities in caloric testing on the ipsilateral side is usually the only abnormal finding, however compression on the cerebellum and flocculus can lead to optokinetic abnormalities. Interestingly this test picks up 98% of tumors involving the superior vestibular nerve but only 60% of patients with tumors involving the inferior vestibular nerve. This is because the superior nerve innervates the lateral semicircular canal which is tested with calorics where the inferior nerve supplies the other two portions of the vestibule (27). Therefore this cannot be used to screen for vestibular schwannomas.

Imaging is really the gold standard for identifying vestibular schwannomas and other CPA tumors. On CT imaging 90% of tumors will enhance with contrast but the diagnostic accuracy is only 63% (28). CT scanning frequently misses tumors that are extracanalicular and tumors not extending >5mm to the CPA. MRI imaging on the other hand is the gold standard for vestibular schwannomas. Tumors preferentially take up gadolinium for visualization of smaller tumors as small as 3mm in size (29). Contrast studies will show a hyperintense signal on both T1 and T2 images but non-contrast studies will show hypointense lesions on T1 and isointense lesions on

T2. Some institutions have used T2 fast spin-echo MRI's as a screening test in those with contrast allergies, but most patients with abnormalities will require a formal study (30).

Because meningiomas are the second most common type of CPA tumor it is important to be able to differentiate it's characteristics from that of a vestibular schwannoma on MRI. Vestibular schwannomas will have more of a globular appearance, centered on the internal auditory canal, and may resemble an ice cream cone. In contrast, a meningioma will likely have more of a sessile appearance with a "dural tail" at the periphery and will be hypointense on T1 images but hyperintense on T2 images.

Differential Diagnosis

As stated previously, meningiomas are the second most common CPA tumor and represent about 3% of all CPA tumors (12). They do not metastasize but do recur due to bony invasion. They are formed from cap cells around the arachnoid villi near dural sinus' and where cranial nerves enter their foramina. Generally these tumors are not intracanalicular and therefore must be much larger to produce hearing loss. Symptoms and signs again depend on the location of the tumor. Intracanalicular tumors usually present similar to vestibular schwannomas. Otherwise they often present with spontaneous nystagmus, facial hypesthesia and gait ataxia. If they extend inferiorly they can produce hoarseness, dysphagia, shoulder weakness and even tongue atrophy (31). Like vestibular schwannomas, hearing tests will show retrocochlear losses and the ABR will be normal in 25% of patients (32). Treatment is surgical but you must remove a rim of normal tissue due to the bony invasion to prevent recurrence.

Epidermoid tumors are histologically the same as cholesteatomas and develop from epithelial rest cells. They are slow growing and often do not present until the second or third decade. These tumors will often follow the path of least resistance and therefore will often be irregularly shaped and quite large before causing symptoms. Facial twitching has been described as a common finding with these tumors and facial weakness is more common than with cranial nerve schwannomas. Workup is again consistent with retrocochlear losses and treatment is surgical excision. Epidermoids can often resemble cysts on MRI examination as they are hypointense on T1 images but are bright on T2. In order to differentiate these lesions from more cystic lesions like an arachnoid cyst, the T1 weighted flair images can be helpful to show the more heterogeneous characteristics of an epidermoid compared to the homogenous look of a cyst.

Facial schwannomas are histologically identical to vestibular schwannomas. They are rarely restricted to the internal auditory canal, commonly have multiple skip lesions, and generally involve part of the geniculate ganglion. Unique characteristics include aural fullness if distal to the geniculate ganglion and facial weakness is not usually present until these tumors are very large. Hearing and impedance testing shows a retrocochlear loss but in addition the stapedial reflex can be lost in these tumors. Treatment is observation until there is significant growth or grade III facial nerve dysfunction and nerve graft repair is commonly performed at the time of resection (1).

Glomus tumors can present with jugular foramen syndrome and involvement of cranial nerves IX-XI. Treatment is surgery. Hemangiomas are usually centered on the geniculate and lead to a progressive facial weakness. Treatment is surgery with primary nerve graft repair.

Arachnoid cysts can often be drained without large operations. Cholesterol granulomas are bright on both T1 and T2 in contrast to cholesteatomas and can often be drained. Embryonic tumors and primary CNS tumors are resected as appropriate.

Management: Observation

Once a CPA tumor is found counseling is of the utmost importance. Often times resection or treatment of these tumors, especially slow growing vestibular schwannomas can leave the patient with more dysfunction than they had prior to treatment. It is with this idea in mind that the options of observation, radiation therapy, and surgery can be offered depending on the circumstances and patient preferences.

If patients opt for observation it is important to let them know what to expect. Average growth rates for vestibular schwannomas are 2mm per year with a range of 0 to 2cm per year (33). A review of multiple studies have shown that about 40% to 80% of tumors will show some growth by 3 years after diagnosis (23) and 14 to 24% of patients who are observed will go on to have some form of treatment (11). Longstanding hearing loss may represent a slow growing tumor and therefore may help guide treatment options (34). Age should not be the only determining factor for which patients receive different treatment options. Younger patients may be able to tolerate a large operation better than the elderly, older patients may outlive any symptoms of their surgery, but all patients regardless of age with life threatening symptoms should be offered some form of treatment. If observation is chosen, MRI should be repeated at least every 6 months if not every 3 months during the first year and then yearly after that to obtain proper growth surveillance.

Management: Radiation/Stereotactic Radiosurgery

Gamma Knife (GK) was first introduced by Leskell in 1969 using a cobalt 60 source. It utilizes 201 ionizing beams of radiation to attack tumors from multiple directions. The LINAC system uses a linear accelerator as its source of electrons, but has much fewer beams of radiation compared to the gamma knife. Both of these modalities require only a single session for treatment. More recently fractionated radiotherapy has been used to catch cells in different stages of the cell cycle for maximal effect. The drawback to fractionated therapy is that it requires multiple sessions for full treatment.

Ultimately the goal of radiosurgery is to arrest tumor growth rather than to shrink it or remove it. Local control is defined as patients treated with radiation, not requiring salvage therapy. When combining all three previously mentioned modalities 87 to 100% local control rates have been published. Despite these numbers approximately 23% of patients will develop a transient increase in tumor size for 6 months up to 5 years due to central necrosis of the tumor (23). Therefore it is important to differentiate true tumor growth from transient swelling post therapy to prevent unnecessary salvage therapy.

In 2005, Hasagawa et al. looked at 317 patients treated with GK therapy and 7.8 years of median follow up. 10 year local control rates were >92% and significantly better in patients with tumors <15cm³, with no brainstem compression, and no 4th ventricle compression (35). Most tumors that progressed did so within the first 3 years post-therapy. Freidman et al. in 2006

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looked at 390 patients treated with LINAC and a median dose of 12.5Gy. Median follow up was 40 months. 5 and 10 year local control rates were 90% and only 1% of patients required salvage therapy. With fractionated therapy being so new, there is a wide variety of study treatments ranging from 15 to 57.6Gy in 3 to 32 fractions. Median follow up over multiple studies has been 48 months and the 5 year local control rate is >90% (23).

When comparing tumor control, tumor growth, and hearing preservation between fractionated therapy and radiosurgery (GK or LINAC), fractionated therapy has shown better ranges looking at multiple studies. Tumor shrinkage however is similar between the two modalities (37).

Initially patients were being treated with 16Gy doses with hearing preservation of only 46%. Lower doses were instituted at 12-13Gy, which led to hearing preservation of 68 to 78% without change in local control rates (23). A study looking at 153 patients followed for a median of 4.2 years showed that useful hearing was preserved in 58% of patients but that tumors <1cm³ had significantly more patients with preserved hearing compared to those with tumors >1cm³ of 75% vs 57% respectively. When comparing radiosurgery to fractionated therapy, one study in 2001 was able to show serviceable hearing preservation at 3 years follow up of 81% versus 33%, GK versus fractionated therapy respectively (39). Facial and trigeminal neuropathy showed similar results compared to hearing preservation. As radiation dose was decreased from 16Gy to 12-13Gy complications decreased (36, 40), and fractionated therapy showed better results than radiosurgery for both complications (37).

Other complications observed with radiation therapy included hydrocephalus (0-11%), tinnitus (0.2-5%), ataxia (1.4-3.6%), vertigo (1.4-1.7%), malignant transformation (0-0.3%), and disequilibrium (33%)(41).

Management: Surgery

When it comes to surgery there are three different options including the translabyrinthine approach (TL), the middle cranial fossa approach (MCF), and the retrosigmoid/suboccipital approach (RS). All surgical options require discussion and collaboration with neurosurgery.

The TL approach has several advantages. It provides an option for resecting a tumor of any size, it has excellent exposure of the posterior fossa, it utilizes the least cerebellar retraction and the facial nerve is easily identified throughout the case. The major disadvantage is the fact that any residual hearing is sacrificed through this approach (42). Control rates with total resection range from 99.5-99.7% (43-44). Near total resection has been described as <25mm² or 2mm thick tumor left in the operative field. Fifty percent of lesions can be visualized on MRI with near total resection and 3% of patients will have a recurrence (45-46).

The MCF approach is one of the approaches that allow hearing preservation. Additionally it provides good exposure of the lateral internal acoustic meatus, CPA and clivus, and drilling is extradural thereby decreasing morbidity. Disadvantages include size limits of tumors <2cm in greatest dimension, extensive temporal lobe retraction, limited exposure of the posterior fossa, and required facial nerve dissection to access tumors (42). Control rates for this technique are 98% (47).

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The RS approach is another hearing preservation procedure and like the TL approach, a tumor of any size can be reached as long as there is less than 2cm of extension into the IAC. Additionally there is wide exposure of the brainstem and lower cranial nerves with consistent identification of the facial nerve throughout the procedure. Disadvantages include increased risk of injury to the endolymphatic sac and vestibular labyrinth with lateral tumors, cerebellar retraction leading to oculomotor and disequilibrium difficulties, and increased risk of air embolism with older positioning techniques (42). Control rates using total resection techniques are 95% with this approach (48).

Serviceable hearing can be preserved in approximately 51% and 31% MCF vs RS approaches respectively (23). Meyer et al in 2006 looked at 162 consecutive patients treated with MCF approach and showed 41% AAO-HNS class A/B hearing and that 50% of patients with word recognition scores greater than 70% preoperatively maintained that level (49). They also showed that as tumor size increased serviceable hearing decreased in an expected manner.

Facial nerve function for microsurgical treatment is best reported at 6 months or 12 months as the gold standard. Patients treated with the RS approach had the best facial nerve function (grade I/II) followed by the MCF and TL approach respectively (91% vs 88% vs 77%) (23). Delayed paralysis has been described where patients have normal postoperative facial nerve function and develop paralysis >72 hours after surgery. The incidence is approximately 5% and 79% of patients will regain normal function by 1 year follow up (50).

CSF leak is more common with patients treated with RS (11%) approach compared to MCF (6%) and TL (8%) approaches and the overall rate is considered to be about 8% (51). Postoperative headache of over 3 months occurs in approximately 10% of patients with RS (21%) approach having the highest incidence compared to MCF (8%) and TL (3%) approaches (51). The most likely reason is due to intradural drilling where bone dust contacts the meninges and CSF leading to aseptic meningitis.

Other microsurgical complications include a mortality of 1% usually due to neurovascular injury. Meningitis occurs in 1-8% of patients with aseptic meningitis being the most common. This can be simply treated with steroids. Bacterial meningitis requires antibiotics and is most commonly caused by *S. aureus*. Tinnitus occurs in about 50% of patients but 50% of patients with preoperative tinnitus will have resolution postoperatively (52). Seizure, hydrocephalus, and stroke represent <2% of cases and are rarely encountered (23).

Microsurgery versus Radiosurgery

Several studies have compared radiosurgery to microsurgery for treatment of vestibular schwannomas. In a retrospective review by Myrseth et al in 2005 with median follow up of 5.9 years, local control rates between microsurgery and gamma knife were not statistically different (89.2% versus 94.2%) (52). Facial nerve function and quality of life were both significantly worse in the surgery group versus the gamma knife group. Gamma knife boasted a facial nerve preservation rate of 94.2% while surgery only showed 79.8% HB grade I/II.

To give further clout to Myrseth's study, Pollock et al. in 2006 performed a prospective cohort of 82 patients treated with surgery versus gamma knife in 82 patients with tumors <3cm

in size. Median follow up was 42 months and local control rates were not significantly different between the groups (96% versus 100%). Despite these findings, facial nerve function/hearing preservation were both significantly worse in those treated with surgery versus those treated with gamma knife (75%/5% versus 96%/63%) (53).

Conclusions

Any patient with unilateral sensorineural hearing loss or tinnitus must be evaluated for possible CPA tumor. Although the differential diagnosis for CPA tumors is quite large, the vast majority are vestibular schwannomas. Vestibular schwannomas less than 3cm in size can be treated with either GK or LINAC radiosurgery, however fractionated radiation is gaining promise and may become the standard of care. If a surgical approach is required and the patient has no serviceable hearing the TL approach is the best option but after that either the RS or MCF approach can be utilized for hearing preservation depending on surgeon preferences. The most important thing to remember when counseling a patient regarding therapy is that treatment of these lesions can often lead to an increase in symptoms or side effects compared to their baseline function. Therefore a candid informed consent is required prior to any therapy of these lesions.

DISCUSSANT: Tomoko Makishima, MD, PhD on Cerebellopontine Angle Tumors with Focus on Vestibular Schwannomas

This was a nicely prepared review of CP angle tumors. There was emphasis on management options, especially regarding newer radiotherapy technology.

Most cases will undergo conservative management and observation. However, for those cases that do undergo surgery, I would like to further emphasize the importance of pre-operative evaluation and consent with the patients. It is very important to explain and make sure the patient understands exactly what to expect after surgery. Many patients have the expectation that their symptoms will get better after surgery, or don't expect it to get worse. Especially, the postoperative outcome regarding dizziness is often unpredictable. It is important to keep in mind that the tumor itself is non-life threatening, and that by performing surgery, you may be causing the patient to end up with more symptoms than before surgery.

And, regarding infections such as cholesterol granulomas, cholesteatomas, and dermoid cysts — the gold standard of treatment is to remove the infection, or obtain a "drainage" pathway. However, given the difficulty reaching the disease, sometimes this will not be feasible, and will result in multiple surgeries.

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