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General

Glossopharyngeal Neuralgia: Epidemiology, Risk factors, Pathophysiology, Differential diagnosis, and Treatment Options

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Purpose of Review

This is a comprehensive review of the most recent literature on glossopharyngeal neuralgia (GPN), a relatively rare form of neuropathic facial pain. It covers the epidemiology, risk factors, pathophysiology, and differential diagnosis given that glossopharyngeal neuralgia can often be confused with other facial pain syndromes. Finally, we extensively review recent findings regarding medical or conservative measures, minimally invasive, and surgical options for potentially treating and managing glossopharyngeal neuralgia.

Recent Findings

An in-depth analysis of the recent literature indicates that glossopharyngeal neuralgia is not only rare but its etiology and pathophysiology are complex and are often secondary to other disease processes. Regardless, current management options are shown to be effective in controlling pain. Conservatively, first-line management of GPN is carbamazepine, but gabapentin and eslicarbazepine acetate are suitable alternatives. In terms of current minimally invasive pain management techniques, pulsed radiofrequency ablation, nerve blocks, or percutaneous radiofrequency thermocoagulation are effective. Finally, surgical management involves microvascular decompression and rhizotomy.

Summary

While there are currently many viable options for addressing glossopharyngeal neuralgia pain ranging from conservative to surgical management, the complex nature of GPN etiology, pathophysiology, and involved anatomical structures prompts further research for more effective ways to treat the disease.

INTRODUCTION

Neuropathic facial pain is produced by a lesion or dysfunction in the central or peripheral somatosensory nervous system that causes significant impairment to an individual's quality of life and may result in medical, dental, social, and psychological burdens.[1,2] Local trauma or systemic disorders can trigger this pain as it causes disruption of structures along the central nervous system neuroaxis to structures in the periphery. Neuropathic pain can be divided into two broad categories: episodic and continuous pain. Episodic neuropathies are defined as paroxysmal, short-lasting, stabbing, or shock-like pain as seen in trigeminal and glossopharyngeal neuralgias. Continuous pain is characterized to be a more constant, dull, achy pain. Examples of continuous pain include peripheral neuritis, persistent idiopathic facial pain, and post-herpetic neuralgia.[1,3]

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Glossopharyngeal neuralgia (GPN), unlike its counterpart, trigeminal neuralgia, is an extremely rare pain syndrome. It produces an electric, shooting pain in the sensory distribution of the auricular and pharyngeal branches of the glossopharyngeal (IX) and vagus (X) cranial nerves. The area of involvement includes the ear, base of tongue, throat, tonsillar fossa, and angle of the jaw. GPN is characterized as a brief, unilateral pain with abrupt onset and cessation that can be easily triggered by simple actions such as talking, swallowing, yawning, and coughing.[4] Touching the external auditory canal and the side of the neck can also elicit pain. An episode can last anywhere from 2 seconds to 2 minutes and can occur up to 200 times per day.[5] Although GPN typically occurs unilaterally, some individuals have described bilateral involvement.[6] Occasionally, GPN has been associated with episodes of syncope, bradycardia, and seizures. When these symptoms occur, GPN is renamed vagoglossopharyngeal neuralgia (VGPN) due to its accompanying involvement of the vagus nerve.[4]

Appreciating the anatomy helps to better understand the symptoms and triggers of GPN. The glossopharyngeal nerve exits the brainstem from the medulla and goes through the jugular foramen to exit the skull.[7] There are five branches of the glossopharyngeal nerve. The tympanic branch not only delivers parasympathetic innervation to the parotid gland, but also provides sensation to the medial surface of the tympanic membrane, the mucosa of the middle ear, and the upper eustachian tube.[8] The stylopharyngeus branch innervates the stylopharyngeus muscle to allow for elevation of the pharynx during talking and swallowing.[7,8] The pharyngeal branch delivers sensory innervation to the pharynx. Together with the vagus nerve, the carotid sinus branch provides parasympathetic innervation from the chemoreceptor in the carotid body and baroreceptors in the carotid sinus which may play a role in the syncopal episodes that occur in VPGN.[4,7] The glossopharyngeal nerve gives off its terminal tonsillar and lingual branches which carry somatosensory and taste from the posterior one-third of the tongue.[9]

Glossopharyngeal neuralgia is diagnosed clinically, but because of its location, clinical features, and rarity, diagnosis is often difficult. It can overlap with other cranial nerve etiologies leading to misdiagnosis. GPN is often misdiagnosed as trigeminal neuralgia (TN) as they share similar clinical features and affect areas that are next to each other.[7] Typically, GPN produces pain on the left side of the body, whereas trigeminal neuralgia affects the right side.[2] Bilateral pain and associations with multiple sclerosis are more common in TN. It is important to note that individuals may suffer from both GPN and TN as the glossopharyngeal nerve can connect with the mandibular division of the trigeminal nerve. Although there may be difficulties with diagnosis, management of GPN is essentially identical to that of TN.[7]

METHODS

We conducted literature searches using PubMed and Google Scholar between October 2020 through March 2021. Articles were chosen based on relevance to glossopharyngeal neuralgia and treatment options. We selected primary literature as well as clinical trial studies to reflect the validity of the review. Older articles were included as well to refer to previous background information.

The PubMed and Google Scholar keywords searched were as follows: glossopharyngeal neuralgia, carbamazepine, pulsed radiofrequency ablation, nerve blocks, or percutaneous radiofrequency thermocoagulation.

EPIDEMIOLOGY

Glossopharyngeal neuralgia is a rare condition that occurs far less than other cranial neuralgias, such as trigeminal neuralgia. It accounts for only 0.2-1.3% of all cranial neuralgias, affecting 0.2-0.4 per 100,000 people per year, with a solidified incidence rate of 0.7 per 100,000 people. The incidence of glossopharyngeal neuralgia increases with increasing age, and most commonly affects adults older than 50 years of age. In a retrospective review of the data on glossopharyngeal neuralgia published in 1981, 57% of the 217 cases studied occurred in patients over the age of 50, and 43% affected ages 18-50. Glossopharyngeal neuralgia occurs equally in both males and females, with no gender predilection, but it is, however, typically observed more often on the left side in females. Spontaneous remission of pain episodes was reported by 74% of patients in the same study previously mentioned, and only 17% had constant pain without relief. 88% of patients reported unilateral pain, while the other 12% had bilateral pain in the sensory distribution of the glossopharyngeal nerve.[10]

RISK FACTORS AND COMORBIDITIES

Glossopharyngeal neuralgia, like trigeminal neuralgia, typically manifests in individuals who are 50 years old and older. Manifestations of GPN increase with age; therefore, age is the primary risk factor for developing GPN. Although there is a higher incidence in females that are affected by pain in the head and neck regions, as well as a higher incidence of females exhibiting orofacial pain, there appears to be no gender preference in GPN. Therefore, both men and women are equally affected in GPN.[11]

In some cases of GPN, patients are found to have cardiovascular or neurological symptoms such as asystole, bradycardia, hypotension, syncope, seizures, or even cardiac arrest. These symptoms result from overlapping connections with the vagus nerve. In even rarer circumstances, patients may develop these signs in the absence of the classic pain symptoms of GPN, making diagnosis even more of a challenge.[7] Other rare comorbidities are tinnitus, vertigo, involuntary movements, and neurovegetative phenomena such as tearing, sweating, salivation, and unilateral mydriasis.[12]

CLINICAL PRESENTATION AND DIAGNOSIS

Clinically, glossopharyngeal neuralgia presents with acute, abrupt onset of repeated episodes of severe, sharp, stabbing unilateral pain in the areas of the sensory distribution of the glossopharyngeal nerve, along with a branch of sensory vagus nerves. These areas include the mastoid, the back of the throat, posterior 1/3 of the tongue, back of the nose,

Eustachian tube and middle ear, tonsils, and voice box. Patients may or may not present with coughing and hoarseness and can have difficulty speaking and swallowing. The pain typically begins at the back of the tongue or throat and radiates to the back of the jaw or ear. Rarely, glossopharyngeal neuralgia can cause bradycardia, hypotension, systole, or even asystole. The longevity of these painful episodes ranges from seconds to minutes, and they may occur many times throughout the day or night. Triggers of pain episodes include, but are not limited to, tinnitus, sudden movement of the head, touching the periodontium, touching the external surface of the ear, coughing, sneezing, swallowing, talking, laughing, or chewing.[13]

Glossopharyngeal neuralgia is typically a clinical diagnosis after presenting with the symptoms listed above. The diagnostic test for glossopharyngeal neuralgia involves touching a cotton swab to the back of the throat, which elicits severe pain that is then relieved with the application of a local anesthetic such as lidocaine or bupivacaine. After the diagnosis has been made, the underlying cause of pain is determined with a complete history of trauma, radiotherapy, previous surgery to the oral and maxillofacial area, lab tests including CBC, CMP, erythrocyte sedimentation rate, and antinuclear antibodies, and finally imaging such as CT scan, MRI, X-Ray, or MR angiogram. The MR angiogram can help to clarify whether vascular compression is the cause by locating the posterior inferior cerebellar artery because it loops up and may compress the supraciliary fossette. If, however, the anterior inferior cerebellar artery is compressed, surgery is needed to formally diagnose glossopharyngeal neuralgia. Finally, a radiograph will diagnose glossopharyngeal neuralgia if it is caused by Eagle's Syndrome.[2]

DIFFERENTIAL DIAGNOSIS

There are numerous diagnoses that contribute to the differential when a patient comes in with acute onset, severe, sharp facial pain, such as glossopharyngeal neuralgia. The list is extensive, and some of the diagnoses that are on the differential will be discussed below. A comprehensive history with a thorough physical exam can often narrow the differential to make a diagnosis, but some type of imaging is frequently required to confirm the suspicion.

TRIGEMINAL NEURALGIA

Trigeminal neuralgia is characterized by sudden onset, unilateral, electric shock-like pain in the distribution of the second or third branch of the trigeminal nerve. The pain is episodic and terminates as quickly as it comes on. It is one of the most common cranial nerve neuralgias, typically affecting elderly females, with an incidence of 4.3 per 100,000 people in the United States. Because it is much more common, glossopharyngeal neuralgia is often misdiagnosed as trigeminal neuralgia. A comprehensive history and physical can aid in proper diagnosis.[2]

SUPRAORBITAL NEURALGIA

Supraorbital neuralgia is a subtype of trigeminal neuralgia that involves the supraorbital branch. It is a rare disorder that typically presents with the following triad: forehead pain that does not radiate, tenderness over the supraorbital nerve when palpated, and relief of symptoms with nerve blockade. Any type of facial pain can fall on the list of differential diagnoses for glossopharyngeal neuralgia, however, the pain associated with supraorbital neuralgia is different in character from which glossopharyngeal neuralgia presents. Patients with supraorbital neuralgia typically have sensory dysfunction and the hallmark is pain that is localized inside or just above the eyebrow.[14]

SUPERIOR LARYNGEAL NEURALGIA

Superior laryngeal neuralgia can be triggered by talking, swallowing, coughing, and yawning, and may also be associated with hoarseness and cough, just like glossopharyngeal neuralgia. For this reason, it is on the list of differential diagnoses. Upon palpation of the superior laryngeal nerve at the location of entrance into the larynx, pain may be evoked. A physical exam in the clinic can help to differentiate between the pain associated with glossopharyngeal neuralgia versus the pain associated with superior laryngeal neuralgia.[15]

NERVUS INTERMEDIUS NEURALGIA

Nervus intermedius neuralgia is a rare disorder, and like glossopharyngeal neuralgia, presents with unilateral electric shock-like, stabbing pain that occurs intermittently. It differs from glossopharyngeal neuralgia, however, in that the pain is located deep in the ear. This pain may be associated with lacrimation, salivation, or taste disorders. It is less common for glossopharyngeal neuralgia to present with shock-like pain deep in the ear, so a comprehensive history and physical exam can help to narrow the differential.[16]

NASOCILIARY NEURALGIA

Nasociliary neuralgia, otherwise known as Charlin's syndrome, nasal nerve syndrome, and nasal ciliary nerve syndrome, presents as an extremely sharp pain in the nasal and paranasal areas. This pain is typically evoked by palpation of the lateral aspect of the nostril. This neuralgia is rare, and the pain primarily radiates to the eyebrow eye, nose, or jaw. Some associated symptoms are tearing of the eyes, conjunctivitis, congestion, sneezing, and erythema on the forehead. Nasociliary neuralgia still presents with facial pain, causing it to be on the differential, however, it affects different parts of the face than a typical glossopharyngeal neuralgia.[17]

OCCIPITAL NEURALGIA

Occipital neuralgia also presents with paroxysmal or shooting/stabbing pain, which also has a deep, aching pain between episodes. Pain can be triggered by palpation of the occipital nerve, and local anesthesia can result in the reso-

lution of symptoms. Associated symptoms of occipital neuralgia include visual impairment, ocular pain, tinnitus, dizziness, and nausea, and because of this, misdiagnoses often occur.[16]

EAGLE'S SYNDROME

Eagle's syndrome presents very similarly to glossopharyngeal neuralgia. It occurs when an elongated styloid process impinges on branches and fibers of the glossopharyngeal nerve, causing the same symptoms. Imaging is required to differentiate between primary glossopharyngeal neuralgia and glossopharyngeal neuralgia symptoms due to an elongated styloid.[8]

TEMPORAL ARTERITIS

Giant cell temporal arteritis presents with headache, painless vision loss, jaw claudication, and fever. There will be some temporal artery tenderness to palpation, and the headache may occur for 2-3 months at a time. This is lower on the differential list for glossopharyngeal neuralgia due to the character of pain that is associated with glossopharyngeal neuralgia and how much it differs from this type of pain, but nonetheless, still needs to be considered in a patient who presents with facial pain. To formally diagnose temporal arteritis, an ESR should be obtained.[18]

JACOBSON'S NEURALGIA

Glossopharyngeal neuralgia can present with only sensory loss at the ear. This is known as the otic form of glossopharyngeal neuralgia, and it is often confused with Jacobson's neuralgia. Jacobson's neuralgia is neuralgia of the tympanic branch of the glossopharyngeal nerve. It presents very similarly to glossopharyngeal neuralgia, however, will require imaging to confirm if there is a mass or other anatomical anomaly that could be causing compression of Jacobson's nerve.[10]

MYOFASCIAL PAIN DYSFUNCTION SYNDROME

Myofascial pain dysfunction syndrome is a psychophysiological disease associated with the muscles of mastication. It presents as an aching, dull, radiating pain that worsens with jaw movement. It has a different type of pain than glossopharyngeal neuralgia, and while it may be lower on the differential, it still falls on the list due to the facial pain that occurs with this syndrome.

CLUSTER HEADACHE

Cluster headache may be the lowest on the list of differentials but is still important to mention. Like glossopharyngeal neuralgia, cluster headaches also occur more commonly in women, and present with unilateral facial pain, but have associated symptoms such as Horner syndrome, conjunctival injection, and epiphora. The attacks are longer than glossopharyngeal neuralgia at 15-180 minutes, rather than seconds to minutes, and attacks occur without any type of stimulation.[19]

PATHOPHYSIOLOGY

The majority of cases of glossopharyngeal neuralgia are idiopathic in which no identifiable lesion can be discovered.[20] Idiopathic causes may be a result of vascular decompression or central pontine dysfunction.[2] One possible explanation for vascular compression of the glossopharyngeal nerve is the posterior inferior cerebellar artery (PICA) compressing the nerve at the level of the root entry zone, as it leaves from the medulla and through the jugular foramen.[21] Demyelination and axon-degeneration of the glossopharyngeal and vagal cranial nerves may be other idiopathic causes of GPN.[7]

Although less commonly attributed to GPN, some individuals may get this pain attacks secondary to other causes. Secondary glossopharyngeal neuralgia may be related to malignancies or lesions compressing the glossopharyngeal nerve. Tumors residing within the cerebellopontine angle (e.g., schwannomas) compress the glossopharyngeal nerve as it exits the skull. Other significant tumors that may cause compression of the nerve include carcinoma of the laryngeal and nasopharyngeal tumors, cranial base tumors, oropharynx tumors, and tongue tumors.[7] Invasion of such tumors may result in engulfment or displacement of the glossopharyngeal nerve leading to worsening of symptoms.[8] Post-radiation treatment may also lead to the development of GPN. In addition, infections such as tonsillitis, pharyngitis, arachnoiditis, parapharyngeal abscess, and tuberculosis may contribute to the pain syndrome. Complications of certain surgical produce (e.g. post-tonsillectomy, post-neck dissection, and post-craniotomy) may result in disturbances of the glossopharyngeal nerve.[2] Certain individuals with syndromes like Eagle's syndrome (elongated styloid process), Paget's syndrome, and Sjogren's syndrome may additionally present with GPN.[7] In particular, bilateral Eagle syndrome was described to be the cause of bilateral GPN in a documented case report.[22] It is theorized that elongation of the styloid process may irritate the glossopharyngeal nerve as it travels medially to the styloid process in the neck.[23] Additional secondary causes include vascular malformations, direct carotid puncture, choroid plexus overgrowth, dental extractions, carotid aneurysms, and occipital cervical malformations.[2,7] There are several etiologies of GPN; thus, it is important to obtain an extensive imaging workup to adequately rule out other pathological processes.

TREATMENT/MANAGEMENT

Treatment of GPN should involve multiple fields of medicine because there are significant differential diagnoses as mentioned above, such as Trigeminal Neuralgia, Temporal arteritis, Jacobson's neuralgia, superior laryngeal neuralgia, and myofascial pain dysfunction syndrome. While the medical management of these disorders might be similar, the surgical approaches after failed conservative treatment are vastly different and must be differentiated.[24] Treatment for this disease can be broken down into three distinct categories that can be initiated in any order based on the severity of symptoms but most commonly follow one. Treatment

usually starts with a highly conservative or pharmacological approach. If that is ineffective, minimally invasive treatment is sought out and then proceeds to surgery as a last resort. These treatments will be discussed as follows.

MEDICAL/CONSERVATIVE MANAGEMENT

One of the first studies performed by Rushton et al in 1981 showed that an anesthetic can be applied locally at the level of the oropharynx which can be both diagnostic and therapeutic for GPN. In the past, medical cocaine was used in addition to the anesthetic, and GPN was diagnosed if the pain was relieved. While this is only a short relief of the pain, it is an option for those with acute symptoms who desire immediate relief. A positive relief of symptoms from the local anesthetic also indicates a good candidate for future surgical intervention if medical management does not work. This study also showed that carbamazepine is favored over phenytoin by patients for the relief of GPN symptoms.[25] Pharmacologic treatment for GPN is very similar to that of trigeminal neuralgia (TN) due to their similar but not widely understood pathophysiology, with both showing relief with anticonvulsants with sodium channel blocking mechanisms.[26] Due to the similarity and lack of studies specifically targeting GPN, studies on TN treatments will be briefly discussed. In a study of rats, carbamazepine was shown to have the most significant reduction in neuralgia-like pain when compared with other similar drugs such as baclofen, clomipramine, and morphine.[27] In a case study of a 48-year-old woman with GPN, it was shown that a two-month trial of gabapentin therapy effectively halted her symptoms for four years, with no side effects to the medication.[28] One group of researchers performed a systematic review to try and determine whether eslicarbazepine acetate (a member of the dibenzoazepine family) would be a suitable alternative for the treatment of neuralgias for those that could not tolerate the first-line treatments such as carbamazepine. One case study they reviewed showed that a woman with TN (bilateral from multiple sclerosis) was able to control her pain with carbamazepine. Unfortunately, she was having significant side effects (symptomatic hyponatremia) that caused her to discontinue the drug. She was, however, able to control the pain with no side effects using eslicarbazepine acetate (400 mg) after a trial of multiple different drugs.[29] Another study retrospectively looked at patients with neuralgia-type pain (5 with TN, 3 with painful diabetic neuropathy, and 2 with postherpetic neuralgia) and showed that patients have a 50% decrease in pain based on a visual analog scale (VAS) after treatment with an average dose of 800 mg per day of eslicarbazepine.[30] Although a few studies showed promising results, the review article concluded that most of the studies did not have a control group and did not have a large enough sample size to endorse the use of eslicarbazepine as a good alternative for carbamazepine in the treatment of neuralgia pain.[31] Another case study of a 78-year-old man with symptoms of glossopharyngeal neuralgia for 2 years concluded with his symptoms being treated with 1800 mg of gabapentin. They tried to use carbamazepine and oxcarbazepine to control the pain but were unsuccessful.[32] Although other medications have been shown to work, the first-line medical treatment continues to be carbamazepine or oxcarbazepine, with medication side effects being the main cause of discontinuation, even though patients are having relief of pain.[33] In addition to these pharmacologic and conservative mechanisms of treatment, additional therapies such as physical and psychological therapy, and compressing both hot and cold have shown differing successes, but can be beneficial to some patients.[34] If medical and conservative treatment fails, minimally invasive techniques are an option.

MINIMALLY-INVASIVE OPTIONS

One option for minimally invasive treatment for those not responding to pharmacotherapy is pulsed radiofrequency (PRF). In this technique, under CT guidance, pulses of radiofrequency are directed at the problematic nerve. This changes how the nerve transmits its electrical signals in a non-ablative manner to reduce the pain that it may be causing. This has been proven to work with patients with GPN symptoms but Jia et al (2020) performed the first retrospective study to determine the long-term outcomes. They concluded that over the long term, pulsed radiofrequency is an efficient and safe treatment option for those afflicted with GPN.[35] Because of the success of pulsed radiofrequency in reducing the painful symptoms of GPN, some researchers wanted to see if performing the same minimally invasive procedure would have a similar outcome in patients with oropharyngeal carcinoma who were experiencing neuralgia due to the same glossopharyngeal nerve. The study looked at 25 patients with oropharyngeal carcinoma and for more than 3 months, the PRF provided a significant reduction in pain and improvement in sleep in 23 of the patients (92%). They concluded that the PRF is a promising method for decreasing pain from GPN that is caused by oropharyngeal cancer.[36]

Another minimally invasive technique that can be used for pain reduction is a nerve block. Liu et al (2019) looked at 12 patients from their hospital with GPN who received a nerve block near the styloid process and concluded that it was a safe, ultrasound-guided treatment that provides a significant reduction in pain for up to 18 months.[37] Another woman with GPN secondary to postherpetic neuralgia experienced several weeks of pain reduction after receiving a nerve block using 2 mL 0.25% bupivacaine and 10 mg dexamethasone and then two more injections at 2 weeks and 4 months.[38]

The last minimally invasive technique to be discussed is percutaneous radiofrequency thermocoagulation (PRT) which has been used for many years as an effective treatment for pain with neuropathic etiology. Wang et al determined that PRT is a safe and effective option for patients with GPN unable to be treated conservatively after contacting 71 patients who received the treatment. They determined that pain relief was experienced by 78.8% of participants immediately after the procedure and 43.0% 10 years after the procedure with little to no complications.[39] Another retrospective study reviewing the same CT-guided PRT treatment looked at 117 cases of GPN who either were failing long-term relief with medical management or who had contraindications to surgery. They concluded that bar-

ring minor side effects to the treatment (such as the larynx and pharynx numbness, hoarseness, and dysphagia which went away by 12.9 +/- 5.1 weeks), there was a significant reduction in pain (using the Barrow Neurological Institute pain scale) for up to 12 years for some patients, indicating a safe and effective treatment option.[40] After trials of minimally invasive techniques, the last resort, which is oftentimes successful, for GPN treatment is surgery.

SURGICAL OPTIONS

The two main surgical options for treatment of glossopharyngeal neuralgia that is refractory to medical management or are medically indicated are microvascular decompression (MVD) and rhizotomy. MVD has been widely used for neuralgia-type pain but until recently the long-term outcomes for treatment of GPN have not been studied. A group in Shanghai reviewed over 200 cases and determined that the pain relief after five years was reported to be "excellent" in 86.9% of patients that answered.[41] Just like any operation, MVD does not come without potential side effects. One common complication experienced by patients is postoperative delirium. Because of delirium's serious nature and potential to cause death, He et al (2019) reviewed over 900 cases of patients with primary cranial nerve neuralgia who received MVD treatment. They wanted to study the patients who experienced postoperative delirium to determine the risk factors so they could preemptively identify those that might be affected to reduce their chances. They found that there are multiple risk factors including being an elderly male, preoperative carbamazepine use, sleep disturbances postoperatively, and hypertension.[42] Using this information, surgeons performing MVD can identify those with the predominant risk factors and stop the delirium from happening, mitigating the deadly risk. To further identify complications of MVD, another group retrospectively analyzed patients receiving the treatment to determine complications within 30 days postop. They concluded there was a 20% complication rate with the majority of said complications being able to be treated without using any invasive methods and not life-threatening. However, they were unable to compare to other literature to understand if 20% is a success rate or not because at the present, there is no standardization in the literature, which the present investigation hopes to clarify.[43]

Another surgical treatment option for GPN is rhizotomy of the glossopharyngeal nerve. Ma et al (2016) retrospectively reviewed 103 cases who either underwent glossopharyngeal rhizotomy alone or had it in combination with a partial vagus nerve rhizotomy. They determined that while both are a safe and effective way of reducing associated pain with long-term pain relief for around 93% of subjects, the combination with vagus nerve rhizotomy had around a 9 times higher complication rate long-term.[44] In some cases, MVD can be attempted along with rhizotomy to achieve pain relief from GPN. Rui et al (2019) compared the treatment option of MVD to MVD with rhizotomy of the glossopharyngeal nerve. They found that there was no significant difference in the cure rates. They also found that there was a higher rate of complications such as a cough associated with drinking and hoarseness with MVD plus rhizotomy. Their study indicates that treatment with the addition of rhizotomy to MVD does not raise the incidence of cure rates of patients with GPN and actually may increase the risk of complications.[45] One group also wanted to see if a rhizotomy was needed after/during the MVD in order to achieve appropriate pain control. They were able to determine that MVD was successful enough on its own with 46 out of 46 patients having immediate postoperative pain relief. They also found that after 1 year, 97.8% of them continued to have excellent pain control.[46] All of the present treatments are summarized in Tables 1-3.

CONCLUSION

Glossopharyngeal neuralgia while rare is a complex pain syndrome that requires multi-faceted management. Many different medical specialties are involved in caring for patients who are affected by glossopharyngeal neuralgia. These specialties include neurology, otolaryngology, interventional pain specialists, and neurosurgery. This review has extensively outlined the epidemiology, risk factors, clinical presentation, diagnostic criteria, differential diagnoses, pathophysiology, treatment, and clinical trials of glossopharyngeal neuralgia. Many other pathologies can present similarly to glossopharyngeal neuralgia, so definite diagnostic measures are required to make the formal diagnosis. The management of glossopharyngeal neuralgia can be medical, minimally invasive, or surgical. Medical management typically includes carbamazepine or oxcarbazepine. Other neuropathic pain medicines can also be given if carbamazepine or oxcarbazepine do not adequately improve pain. Glossopharyngeal neuralgia can also be treated with interventional pain management techniques, most commonly in the form of a pulsed radiofrequency ablation, nerve blocks, or percutaneous radiofrequency thermocoagulation. There are two main surgical approaches that can be taken to treat glossopharyngeal neuralgia: microvascular decompression and rhizotomy. Overall, there is a variable prognosis of glossopharyngeal neuralgia because it is largely patient-dependent. Most patients only suffer a single paroxysmal pain episode, with only 25% of patients requiring surgery for long-term relief and the rest being treated with medical management. Bilateral pain, multiple severe pain episodes, or unremitting pain are indicators of poor prognosis.[10] Further research is warranted because glossopharyngeal neuralgia is such a rare disease process, and more forms of management should be investigated in the future.

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Table 1. Medical management of glossopharyngeal neuralgia

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Rushton *et al.* (1981)[25]	217 adults diagnosed with glossopharyngeal neuralgia were managed medically. If treatment was unsuccessful, surgery was performed for potential relief of symptoms	18 patients took phenytoin, with only 2 having enough relief to avoid surgery 20 patients took carbamazepine alone, with only 4 having enough relief to avoid surgery 129 patients had surgical treatment: 110 patients had relief of pain	Carbamazepine is the favored medication for medical treatment Surgery is an effective option for treatment of GN
Deseure *et al.* (2017)[27]	72 rats with infraorbital nerve chronic constriction injury (a model for trigeminal neuralgia) were treated with a continuous 1 week infusion of either 30 mg/day of carbamazepine, 1.06 mg/day baclofen, 4.18 mg/day clomipramine, and 5 mg/day morphine and observed on spontaneous or evoked pain behavior	Face grooming (a measure of pain associated with trigeminal neuralgia) was shown to be reduced in those receiving carbamazepine and baclofen. Clomipramine and morphine treated showed no significant reduction in face grooming All drugs tested exhibited antiallodynic effects	Carbamazepine exhibited the strongest effects in reducing neuralgia-like pain This can confirm the use of carbamazepine as a first line pharmacologic treatment for glossopharyngeal neuralgia.
Moretti *et al.* (2002)[28]	Case Study of a 48 year old woman with GN followed for four years with various medical treatments	After a trial of Carbamazepine, Ketolorac, and a steroid, Gabapentin was initiated at 400 mg six times daily for 2 months. After stopping the therapy, patient was asymptomatic for 4 years	Gabapentin is a viable treatment option for GN therapy
Gaber *et al.* (2013)[29]	Case Report of a 62 year old female with refractory TN and multiple sclerosis who had to discontinue carbamazepine due to symptomatic hyponatremia	After trials of gabapentin, amitriptyline, and topiramate with no significant relief of pain, 400 mg of eslicarbazepine per day provide relief of TN pain with no medication side effects.	Eslicarbazepine is a potential option for those with neuralgia type pain who cannot take first-line medications due to side effects.
Garcia *et al.* (2014)[30]	Retrospective observational study on 10 patients to determine pain reduction from neuropathic-type pain with use of eslicarbazepine acetate (5 with TN, 3 with painful diabetic neuropathy, and 2 with post herpetic neuralgia)	An average dose of 800 mg/day was given to each patient. Maximum dose was 1,200 mg/day in one case. After 3 months, there was a reduction of at least 50% in pain according to a visual analog scale (VAS).	Eslicarbazepine is a potential option for those with neuralgia type pain
Simpson *et al.* (2019)[47]	Case study of 78year old man with GN symptoms for 2 years. Trials with carbazepine and oxcarbazine were unsuccessful	The patient's pain as able to be controlled with 1800 mg per day of gabapentin	Gabapentin is a suitable option for treatment of GN pain for those unable to handle the side effects of the first-line treatments carbamazepine and oxcarbazine.

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Table 2. Minimally invasive management of glossopharyngeal neuralgia

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Jia *et al.* (2020)[35]	A group of 30 patients with idiopathic GN treated with CT guided radiofrequency ablation were retrospectively investigated to determine the long-term outcomes of the treatment	Those with satisfactory pain relief: 93.3% at 12 months 89.6% at 24 months 85.3% at 36 months 79.6% at 48 months 73.0% at 60 months 73.0% at 72 months 54.8% at 84 months 54.8% at 108 months 54.8% at 120 months	Pulsed Radiofrequency is a safe and effective treatment option for those with GN that have failed medical management.
Bharti *et al.* (2018)[36]	A group of 25 patients with pain in the distribution of the glossopharyngeal nerve underwent fluoroscopy guided pulsed radiofrequency (PRF) ablation.	Significant reduction in site specific pain, odynophagia, and ear pain for all patients. All patients also reported better sleep, decreased nausea and vomiting, and lesser opioid consumption. Pain relief lasted an average of 5-9 months.	PRF is safe and effective at reducing pain in patients with oropharyngeal carcinoma causing GN.
Liu *et al.* (2019)[37]	A total of 12 patients from First People's Hospital with GN who received an ultrasound guided nerve block (total of 48 injections with 0.5% lidocaine and 40 mg methylprednisolone) were retrospectively analyzed to determine pain reduction.	Pain relief effective rate (determined by decrease in VAS score by >2 points): Discharge – 83.3% 6 months – 83.3% 12 months – 58.3% 18 months – 33.3%	Ultrasound guided nerve block of the glossopharyngeal nerve is a safe and effective treatment option for those experiencing GN who have failed medical management
Schuster *et al.* (2018)[38]	A 51-year-old woman diagnosed with glossopharyngeal shingles who failed medical management received a fluoroscopic guided glossopharyngeal nerve block.	After a nerve block with 2 mL 0.25% bupivacaine and 10 mg dexamethasone and then one again at 2 weeks and then 4 months after that, the patient experienced multiple weeks of significant pain relief from the GN.	A glossopharyngeal nerve block was effective at reducing pain from GN in at least one woman with postherpetic neuralgia.
Wang *et al.* (2016)[39]	A total of 71 patients with GN were retrospectively analyzed after receiving CT guided percutaneous radiofrequency thermocoagulation (PRT) for pain reduction.	Pain reduction (determined by telephone): Immediate post-op: 78.8% Those remaining in "excellent" or "good" pain relief: 73.2% at 1 year 63.0% at 3 years 53.2% at 5 years 43.0% at 10 years	CT guided PRT is a safe and effective method for long term pain relief in those suffering from GN who have failed medical management.
Song *et al.* (2019)[40]	A total of 117 patients with GN were retrospectively analyzed after receiving treatment with CT guided PRT.	82.1% of patients had "excellent" relief of pain immediately following intervention Those experiencing "excellent" pain relief: 75.9% at 1 year 63.0% at 3 years 54.0% at 5 years 44.2% at 10 years 39.3% at 12.5 years Adverse events due to intervention that were resolved by 12.9 +/- 5.1 weeks: abnormal sense of taste, larynx and pharynx numbness, hoarseness, and dysphagia.	CT guided PRT is a safe and effective method for long term pain relief in those suffering from GN who have failed medical management.

Table 3. Surgical management of glossopharyngeal neuralgia

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
He *et al.* (2019)[42]	A total of 912 patients who received microvascular decompression (MVD) for their primary cranial nerve neuralgias were retrospectively analyzed to determine if they had post-operative delirium in order to determine the risk factors.	Nearly 24% (221) of the 912 patients experienced post-operative dementia. The risk factors were determined to be: "old age, male sex, hypertension, preoperative carbamazepine use, postoperative sleep disturbance, and tension pneumocephalus"	These risk factors can be used to preemptively stop a potentially deadly delirium in those affected before undergoing microvascular decompression for a cranial nerve neuralgia.
Bartek *et al.* (2016)[43]	A group of 98 adult patients with cranial nerve pain who were treated with MVD were retrospectively analyzed to determine complications after 30 days using a standardized form.	Overall complication rate: 20% Grade I: 14% Grade II: 5% Grade III: 1% (Using Landriel Ibanez classification for neurosurgical complications)	They concluded there was a 20% complication rate with the majority of said complications being able to be treated without using any invasive methods and not life threatening. However, they were unable to compare with other literature to know if 20% is a successful rate or not because as of yet, there is no standardization in the literature, which this study hopes to accomplish.
Ma *et al.* (2016)[44]	103 patients with GN were treated with either glossopharyngeal rhizotomy (GPNR) alone or had it in combination with a partial vagus nerve rhizotomy (GPNR+VNR) and retrospectively analyzed	Only 79 of 103 could be contacted 38 GPNR alone: Immediate pain relief: 94.7% Immediate complication rate: 7.9% Long-term pain relief: 92.3% Long-term complications: 3.8% 65 GPNR+VNR: Immediate pain relief: 93.8% Immediate complication rate:4.6% Long-term pain relief: 94.3% Long-term complications: 35.8%	While both are a safe and effective way of reducing associated pain with long-term pain relief for around 93% of subjects, the combination with vagus nerve rhizotomy had around a 9 times higher complication rate long-term.
Xia *et al.* (2017)[41]	228 patients with GN were treated with MVD and then retrospectively analyzed to determine long-term outcomes	Immediate post-op outcome: 89.5% - excellent 5.3% - good 2.6% - fair 2.6% - poor >5-year follow-up (107 cases): 86.9% - excellent 5.6% - good 2.8% fair 4.7% - poor	MVD is an effective and safe treatment option for long-term relief of GN.

Rui *et al.* (2019)[45]	Patients with GN were retrospectively analyzed after treatment with MVD or MVD plus rhizotomy of the glossopharyngeal nerve (MVD + GNR). Twenty-two patients were treated with MVD alone and 15 patients were treated with MVD + GNR.	MVD alone: 19 cases cured 3 cases improved • Complications: ◦ 2 hoarseness (short-term) and drinking induced cough, 1 CSF leakage, 1 intracranial infection, 1 ipsilateral hearing loss MVD + GNR: 14 cured 1 improved • Complications ◦ 2 permanent hoarseness, 4 drinking induced cough (short-term) and hoarseness, 1 ipsilateral facial paralysis, 1 CSF leakage No significant difference was noted.	No significant difference in the cure rates. Higher rate of complications such as a cough associated with drinking and hoarseness with MVD + GNR. Their study indicates that treatment with the addition of rhizotomy to MVD does not raise the incidence of cure rates of patients with GN and actually may increase the risk of complications.
Funct *et al.* (2020)[46]	A total of 46 patients with GN unable to be treated medically were treated with MVD. A retrospective analysis was performed to determine whether MVD alone without rhizotomy was enough to control their pain.	100% of patients had immediate post-operative pain relief after MVD alone. After 1 year, only one patient had occasional return of pain.	MVD by itself without rhizotomy is a safe and effective treatment option for those with a painful GN that is unable to be managed medically.

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