Neuroscience
Journal

A new concept of
Parkinson's disease

Tumors of the anterior skullbase

As physician co-leaders of Palmetto Health's neuroscience service,

we share a vision to provide the most advanced neurology and neurological surgery treatments available to the residents of South Carolina. We are excited to share this latest edition of our neuroscience journal featuring articles about tumors of the anterior skullbase and a new concept in Parkinson's disease as a prion disorder.
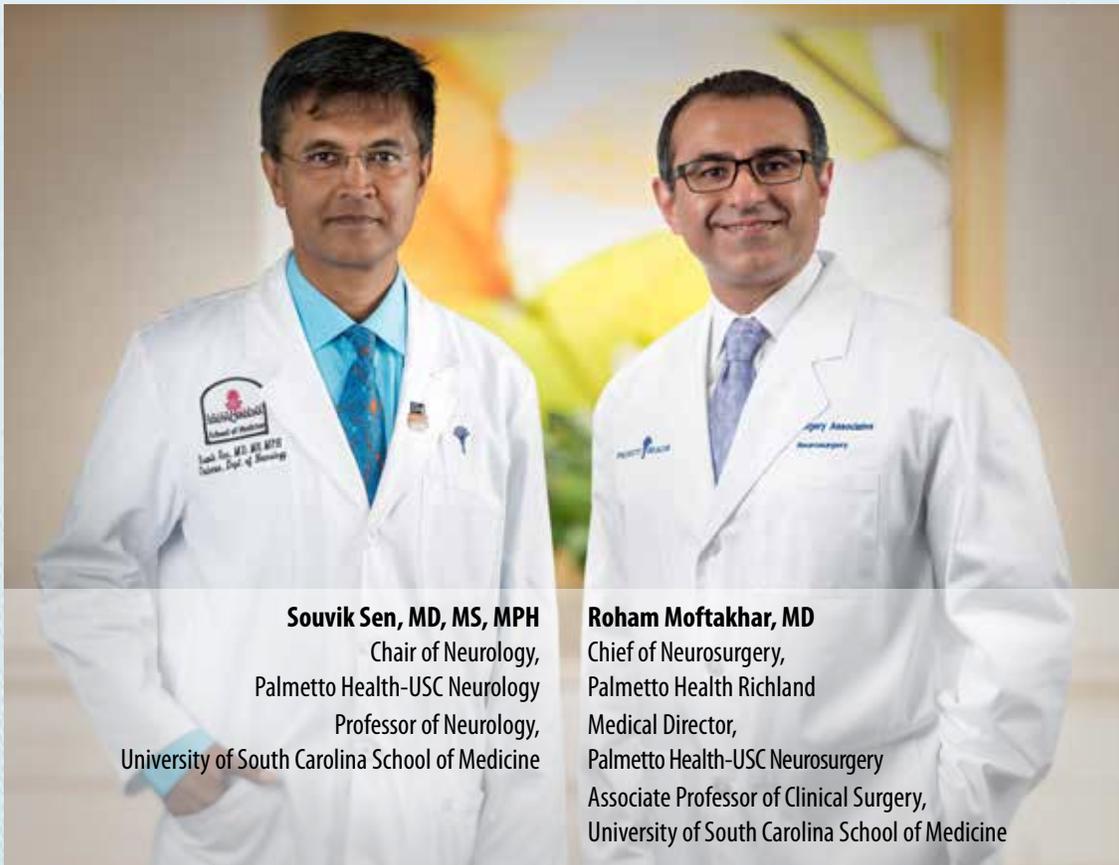
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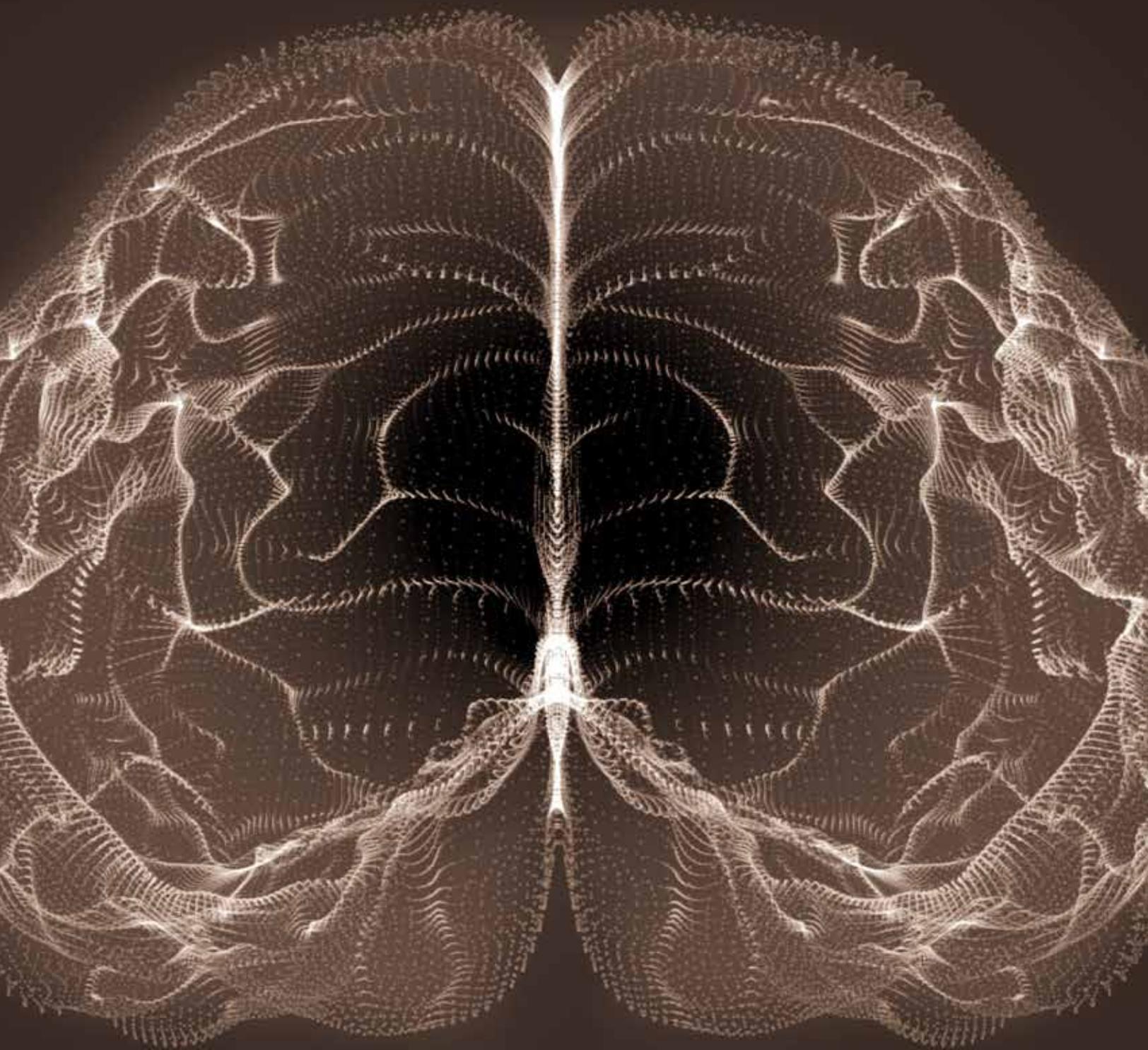
A new concept of Parkinson's disease as a prion disorder

by Pornpimol Becky Anprasertporn, MD, Palmetto Health-USC Neurology

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease. In the United States, it affects more than one million people and there are approximately 60,000 newly diagnosed cases each year. Studies show an incidence rate of 160 per 100,000 population over age 65 in developed countries[1]. Age is the most important risk factor, in combination with environmental exposure, oxidative stress and susceptible genes. The monogenic form of PD, however, only accounts for 3-5 percent of sporadic cases but it can be more prevalent in certain parts of the world[2].

Pathophysiologically, PD is characterized by a loss of dopamine-producing neurons in the substantia nigra pars compacta (SNc), which results in decreased dopamine input to the striatum and increased total inhibition output of the basal ganglia pathway back to the thalamus and cerebral cortex. This gives rise to cardinal symptoms of PD, especially akinesia or bradykinesia, the most essential components for diagnosis of PD. The histopathologic hallmarks of PD are intracytoplasmic proteinaceous inclusions in neurons and their terminals, known as Lewy bodies and Lewy neurites. Lewy bodies are formed by misfolded alpha (α)-synuclein proteins.
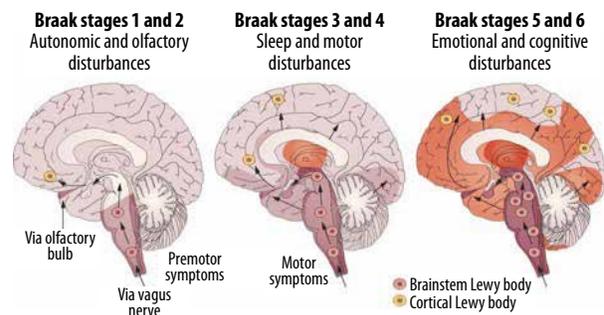

Braak stages 1 and 2
Autonomic and olfactory disturbances

Braak stages 3 and 4
Sleep and motor disturbances

Braak stages 5 and 6
Emotional and cognitive disturbances

Via olfactory bulb

Premotor symptoms

Via vagus nerve

Motor symptoms

⦿ Brainstem Lewy body
⦿ Cortical Lewy body

FIGURE 1 | Braak pathological staging of Parkinson's disease-Permission granted from John Wiley and Sons

Misfolded α-synuclein behaves like a prion protein

The Braak pathological staging of PD demonstrated that in early stages or the prodromal phase of the disease (stage 1 and 2), Lewy bodies initially form in olfactory bulbs and the dorsal motor nucleus of the vagus nerve in the medulla. In patients it clinically manifests as hyposmia and constipation, which are common premotor symptoms that can precede motor symptoms for a few decades. The Lewy bodies and Lewy neurites then spread to the brainstem reticular complexes, nucleus ceruleus, raphe nucleus and substantia nigra in the middle stages (stage 3 and 4), causing rapid eye movement behavior disorders (REMBD), depression and motor symptoms, respectively. In the later stages (stage 5 and 6) they further spread to the limbic system and finally neocortices, causing neurobehavioral and cognitive disturbances[3] (Figure 1). How they

propagate from one body region to another is still not well understood. This question has been extensively studied for decades. In 2009, there was an emerging idea of a "prion disease hypothesis" of misfolded α -synuclein proteins by Olanow, Pruisner and Desplat[4-6] who suggested that misfolded α -synuclein proteins act like misfolded prion proteins. This theory is supported by the interesting autopsy findings from PD patients transplanted with fetal nigral mesencephalic cells 10 to 14 years prior that revealed the development of typical Lewy body pathology within previously unaffected grafted neurons[5]. This theory has been a very hot topic in PD since then.

α-synuclein is a neuronal protein mainly located in the presynaptic terminals and axons. Its exact functions are not well understood but may involve in synaptic vesicle transport, stabilization of SNARE (soluble N-ethylmaleimide-sensitive factor attachment receptor) complex family proteins and brain lipid metabolism[5-7]. Under natural conditions, α-synuclein is conformed in an α-helical structure and intrinsically unfolded at neutral pH and temperature. Misfolded α-synuclein protein due to various etiologies forms beta (β) sheet conformation which further promotes misfolding of wild type α-synuclein proteins in a chain reaction and interferes with lysosomal and proteasomal clearing function. This leads to the formation of toxic oligomer and amyloid fibril aggregates in neurons and glial cells in form of Lewy bodies and Lewy neurites. The aggregation of toxic oligomers and fibrils can transmit from cell to cell via conventional endocytosis, axonal transport, and furthermore, jumping through synapses, causing spreading of abnormal protein aggregation throughout the brain, which leads to neurodegeneration[5-8]. Interestingly, duplication or triplication of the wild type α-synuclein gene can also cause conformational changes. This indicates that increased levels of the mutant or wild-type

α-synuclein proteins are sufficient to cause the disease. New evidence also found that besides α-synuclein, abnormal tau and TDP-43 proteins also have prion-like properties[8].

The conformational change and transmission process of α-synuclein proteins are very similar in manners to prion proteins. The term "prion" refers to abnormal pathogenic agents that are transmissible and are able to induce abnormal folding of specific normal cellular proteins called "cellular prion proteins (PrP^C)" that are found most abundantly in the brain. Prion diseases or transmissible spongiform encephalopathies (TSEs) are a family of rare progressive neurodegenerative disorders that can affect both humans and animals. Prion diseases in humans include Creutzfeldt-Jakob disease, Gerstmann-Straüssler-Scheinker disease, familial fatal insomnia and kuru.

The function of PrP^C is unknown. The PrP^C has a largely α-helical conformation and resides on the surface of cell membranes. The misfolded PrP^C isoform such as PrP^{Sc} (Sc stands for scrapie) aquires a high β-sheet content and assembles into toxic oligomers and rods that coalesce to form prion amyloid plaques. Similarly, the PrP^{Sc} protein acts as a template to promote further conformational change of the PrP^C proteins and can be transmitted from affected to healthy unaffected nerve cells, in which the sequence is recapitulated, thereby extending the neurodegenerative process[6]. The similarity of the misfolded α-synuclein and prion proteins' behaviors are illustrated in Figure 2.

Implications of the prion hypothesis of PD for a neuroprotective therapy
Understanding the pathogenesis mechanisms of how α-synuclein proteins misfold, aggregate and transmit from cell-to-cell can guide us toward potential novel therapies for PD. There were several ideas such as stabilizing α-synuclein to prevent it from misfolding, knocking out

native α-synuclein to eliminate substrates for misfolding, enhancing misfolded protein clearance through the lysosomal system, blocking the prion conformer chain reaction or inhibiting aggregation of intracellular proteins[5, 8]. There was a report that use of a monoclonal antibody against misfolded α-synuclein can block the propagation of α-synuclein in wild-type mice after intracerebral inoculation of α-synuclein fibrils by directing extracellular α-synuclein to microglia for degradation[5, 8]. Likewise, In Alzheimer's disease, there were many clinical trials of vaccination of amyloid beta (Aβ) peptides or immunotherapies with Aβ antibodies, which seemed to be effective in clearing amyloid plaques but failed to improve clinical symptoms and tau pathologies[8]. Even though immunotherapy and gene therapy seem to be very promising, we still require many more ancillary studies especially in terms of clinical outcome correlation. It is still unknown whether and what the consequences and side effects there will be if α-synuclein gene is knocked out or knocked down. It is also possible that a neuroinflammation process can cause abnormal protein aggregation, damage the cellular membrane, impair the blood brain barrier and promote cell-to-cell transmission so anti-inflammatory or antioxidant therapy may also be beneficial[7]. Hopefully, we will be able to achieve the effective neuroprotective methods of PD in the near future. ◄
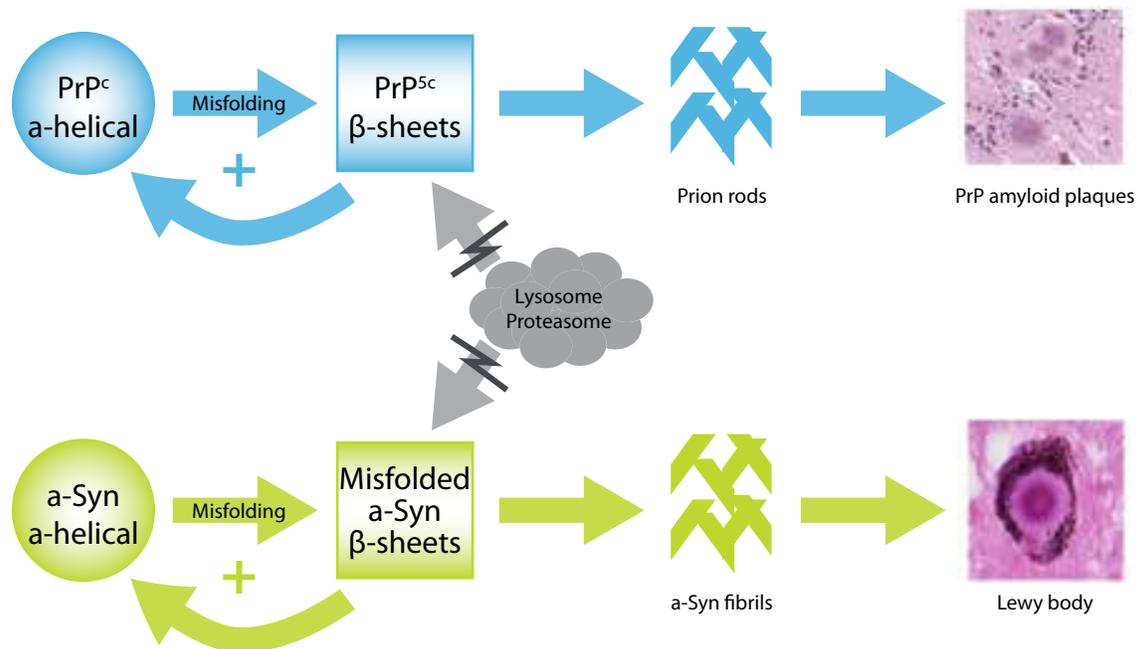

FIGURE 2 | Similarities of prion and α-synuclein proteins in their natural conformations and behaviors of their misfolded forms in further promoting misfolding of wide-type proteins, aggregation and cell-to-cell transmission

References
1. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. The Lancet Neurology. 2016;15(12):1257-72.
2. Klein C, Westenberger A. Genetics of Parkinson's disease. Cold Spring Harbor perspectives in medicine. 2012;2(1):a008888.
3. Halliday G, Lees A, Stern M. Milestones in Parkinson's disease--clinical and pathologic features. Movement disorders : official journal of the Movement Disorder Society. 2011;26(6):1015-21.
4. Desplats P, Lee HJ, Bae EJ, Patrick C, Rockenstein E, Crews L, et al. Inclusion formation and neuronal cell death through neuron-to-neuron transmission of alpha-synuclein. Proceedings of the National Academy of Sciences of the United States of America. 2009;106(31):13010-5.
5. Olanow CW, Brundin P. Parkinson's disease and alpha synuclein: is Parkinson's disease a prion-like disorder? Movement disorders : official journal of the Movement Disorder Society. 2013;28(1):31-40.
6. Olanow CW, Prusiner SB. Is Parkinson's disease a prion disorder? Proceedings of the National Academy of Sciences of the United States of America. 2009;106(31):12571-2.
7. Chu Y, Kordower JH. The prion hypothesis of Parkinson's disease. Current neurology and neuroscience reports. 2015;15(5):28.
8. Hasegawa M, Nonaka T, Masuda-Suzukake M. Prion-like mechanisms and potential therapeutic targets in neurodegenerative disorders. Pharmacology & therapeutics. 2016.

Tumors of the anterior skullbase

by David C. Straus, MD, Palmetto Health-USC Neurosurgery

Skullbase surgery encompasses a variety of pathologies that include tumors arising from the covering of the brain and the cranial nerves. This region of the body involves a complex interface between the spine, the hearing apparatus, the nasal sinuses and the soft tissues of the neck. At Palmetto Health-USC Neurosurgery, we provide the most advanced, multidisciplinary care for diseases of this region, including rhinologists, otologists, endocrinologists, neuro-ophthalmologists, radiation oncologists and fellowship-trained skullbase neurosurgeons.

The skullbase can be conceptually divided into three different regions: the anterior skullbase, which is intimately connected to the nasal sinuses, pituitary gland and visual apparatus; the lateral skullbase, which is related to the structures to the hearing apparatus and the surrounding nerves; and the posterior skullbase, which relates to the structures in the region where the head connects to the spine.

In this article, I will discuss some commonly encountered pathologies of the anterior skullbase and review examples of cases I have treated in the past six months to demonstrate how our team approach can optimize care for patients with tumors affecting this complex region of the body.

Meningiomas

Meningiomas are benign tumors that grow from the arachnoid cap cells of the covering of the brain--the meninges. While meningiomas have very low risk of malignancy, significant morbidity and even mortality can result from their propensity to grow and cause compression of important parts of the brain, nerves and surrounding structures. These tumors can grow in many parts of the skull and cause a plethora of different symptoms based on the location. There are three distinct locations along the anterior skullbase where these tumors may grow: the olfactory groove, the planum sphenoidale and the tuberculum sellae.

Meningiomas exhibit variable growth rates. Patients who do not exhibit clear symptoms, or whose critical structures are not imminently at risk, often may be monitored with a strategy of watchful waiting. For tumors that show progressive growth or have become symptomatic, surgical removal is recommended to prevent further neurologic injury. The more anterior the tumor the later symptoms tend to arise; thus, olfactory groove meningiomas (Figure 1, yellow) may grow to large sizes before causing symptoms, which may include seizures, personality changes from frontal lobe dysfunction and loss of smell from encasement of the olfactory nerves. Planum sphenoidale meningiomas (Figure 1, blue), with their closer proximity to the pituitary gland, major intracranial blood vessels and optic apparatus, tend to be of intermediate size at the time of symptom onset and diagnosis. Finally, tuberculum sellae meningiomas (Figure 1, red), growing in a very confined space just beneath the optic chiasm, tend to cause symptoms, particularly of visual loss or pituitary dysfunction very early in the course of their growth.
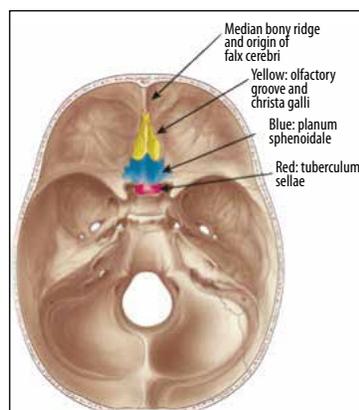

Median bony ridge and origin of falx cerebri

Yellow: olfactory groove and christa galli

Blue: planum sphenoidale

Red: tuberculum sellae

FIGURE 1 | Site of origin for anterior skullbase meningiomas.

Olfactory groove meningioma:

A 58-year-old female presented to the ER with a new onset seizure. Upon further questioning, it was noted she had a three-month history of personality changes, forgetfulness and headaches. Evaluation in the emergency room revealed a giant olfactory groove meningioma causing compression and edema in both frontal lobes (Figure 2).

Given her clear symptomatology and the large size of her tumor, surgical removal was recommended. After careful planning, a stereotactically navigated bifrontal craniotomy was performed. Microsurgical techniques were used to remove the tumor while avoiding injury to the compressed frontal lobes.

She had an excellent recovery and was discharged from the hospital two days after surgery. Three months later, her personality changes and memory improved significantly and she has remained seizure-free.

Planum sphenoidale meningioma:

A 55-year-old female was found to have an anterior skullbase meningioma. She underwent a right frontotemporal craniotomy and orbitotomy to remove the meningioma of the planum sphenoidale. A complete resection of the tumor was achieved (Figure 4B).

A 44-year-old male, who presented with a grand-mal seizure, was found to have a meningioma affecting both the planum sphenoidale and the tuberculum sellae. He did not have visual loss at the time of presentation, though there was encroachment of the tumor onto the pituitary gland and into both optic canals, indicating a critical risk of future visual impairment. He underwent a right frontotemporal craniotomy, orbitotomy and bilateral optic nerve decompressions. Using this approach, we were able to completely resect the tumor and open the fibrous and bony constrictions around the optic nerves as they enter the orbit to minimize any future risk of visual loss in the event of tumor recurrence.
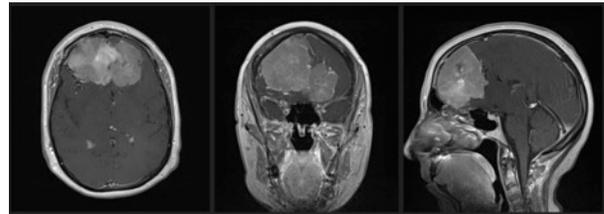

FIGURE 2 | Giant olfactory groove meningioma. Pre-op T1-weighted MRI with contrast.
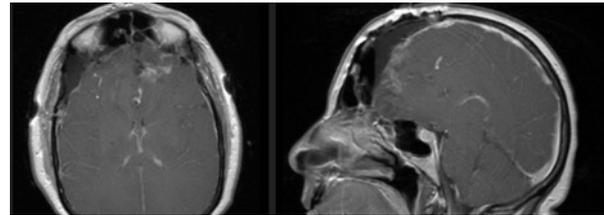

FIGURE 3 | Immediate post-op T1-weighted MRI with contrast showing complete resection of giant olfactory groove meningioma through a bifrontal craniotomy.
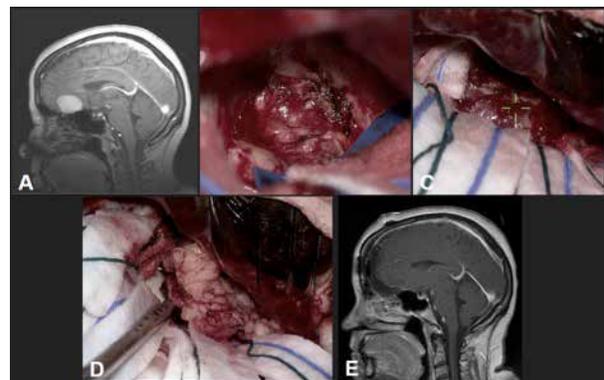

FIGURE 4 | A) Pre-op imaging of planum sphenoidale meningioma. B-D) Intraoperative view of exposed tumor capsule, devascularization and internal debulking of tumor. E) Post-op imaging showing complete resection of planum sphenoidale meningioma using a right frontotemporal craniotomy with orbital osteotomy.

Tuberculum sellae meningioma:

A 69-year-old male presented with severe visual impairment over the course of five months. He was found to have a moderate-sized tuberculum sellae meningioma compressing his optic nerves and chiasm on the left > right side. He underwent a right frontotemporal craniotomy, orbitotomy and bilateral optic nerve decompressions and complete resection of the tumor using this approach.

Pituitary Adenomas

Pituitary Adenomas are benign growths that originate from cells within the pituitary gland. They may secrete hormones that can cause severe medical problems such as hypercortisolism
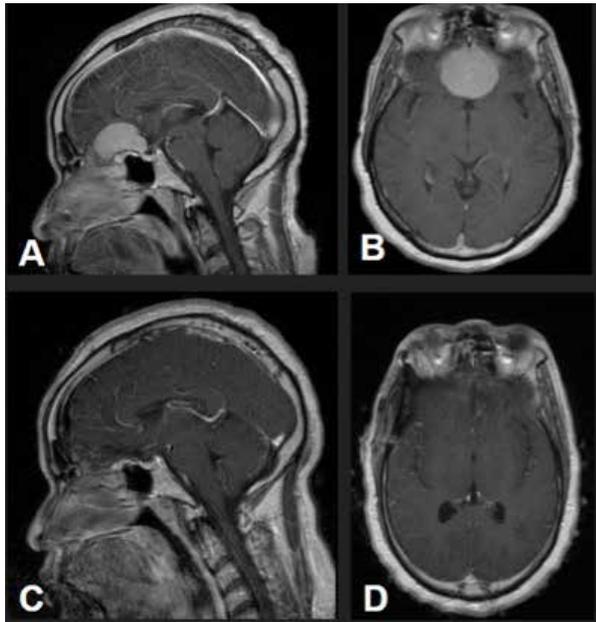
FIGURE 5 | A-B) Pre-op imaging showing meningioma of anterior skullbase involving both planum sphenoidale and tuberculum sellae. C-D) Post-op imaging showing complete resection using a right frontotemporal craniotomy with orbital osteotomy.
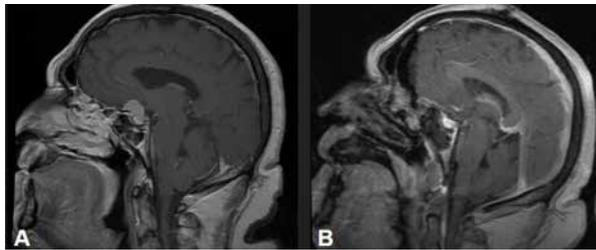

FIGURE 6| A) Pre-op imaging showing tuberculum sellae meningioma compressing left optic nerve and optic chiasm. B) Post-op imaging showing complete resection using a right frontotemporal craniotomy with orbital osteotomy.
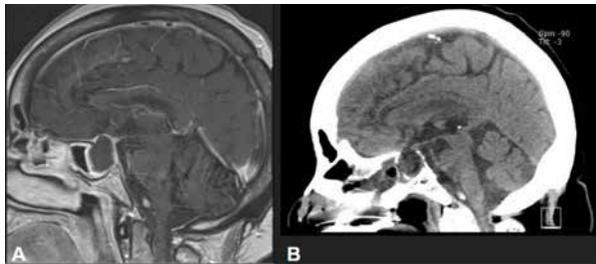

FIGURE 7 | A) Pre-op imaging showing sellar and suprasellar mass compressing the optic chiasm. B) Post-op head CT showing the endoscopic endonasal transsphenoidal approach though opening in the sphenoid sinus and complete resection with resolution of mass effect on the optic chiasm.
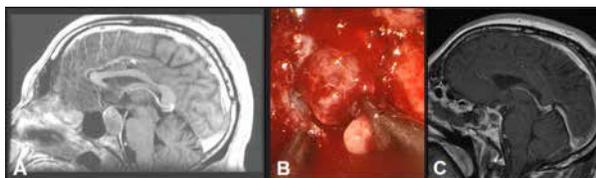

FIGURE 8 | A) Pre-op imaging showing sellar and suprasellar mass compressing the optic chiasm. B) Intraoperative photo showing transsphenoidal exposure of the sella and tumor being removed. C) Post-op imaging showing complete resection using an endoscopic endonasal transsphenoidal approach with preservation of the pituitary stalk and native gland.

(Cushing's disease) and acromegaly. The secreting tumors often are smaller than non-secreting tumors because their endocrinologic symptoms may lead to an earlier diagnosis. A particular subtype of hormone secreting tumor, the prolactinoma, often has excellent response to medical treatment. Non-secreting tumors and large secreting tumors (besides prolactinomas) often require surgical treatment, particularly if there is loss of vision from compression of the optic chiasm, which sits directly above the pituitary gland. Evaluation requires a hormonal panel and visual field testing. Of the patients who require surgery for tumor removal, many can be treated with a minimally invasive endoscopic endonasal approach. This uses the natural orifice of the nares to gain access to the pituitary gland through the air sinuses at the base of the skull. In certain cases, particularly with a tumor spreading laterally and/or anteriorly, either an expanded endonasal approach or a craniotomy may be required to gain adequate access to the tumor.

Pituitary Case 1
A 69-year-old female with multiple medical comorbidities – who presented with headaches, acute onset of a right third nerve palsy and bitemporal hemianopsia – was found to have a nonsecreting sellar and suprasellar mass compressing the cavernous sinus on the right and the optic chiasm. An endoscopic endonasal transsphenoidal approach was achieved working closely alongside our ENT-rhinologist. The tumor was completely removed without an intraoperative CSF leak. Because of the large tumor size, a nasoseptal flap was used for the reconstruction. She made an excellent recovery with resolution of her third nerve palsy in the first week after surgery and improvement in her headaches and bitemporal hemianopia.

Pituitary Case 2
A 55-year-old male presented with headaches and intermittent blurred vision. He was found to have a sellar/suprasellar mass that did not show evidence of hormonal secretion. He did not have

any definite visual field loss, but given the large suprasellar extension and clear radiographic compression of the optic nerves, he opted for surgical removal. We used the endoscopic endonasal transsphenoidal approach to remove this tumor in its entirety, and were able to do so without an intraoperative CSF leak. Using this approach, we preserved the native pituitary gland and stalk, optimizing his chances of retaining full pituitary function and hormonal control.

Craniopharyngiomas

Craniopharyngiomas are less common tumors of the parasellar region that occur in a bimodal distribution, primarily affecting adolescents and middle-aged adults. These tumors originate from remnants of the embryonic tissue in the pituitary stalk. They often cause visual loss from compression of the optic chiasm and tracts. They also may cause hydrocephalus from obstruction of CSF flow in the third ventricle and hypothalamic dysfunction. The consistency of craniopharyngiomas may vary from being extremely cystic, to soft tissue to very firm and densely calcified. Surgical resection is the first-line treatment. In cases of recurrent or residual tumors, stereotactic radiosurgery may be used to prevent further growth of the tumor. In tumors with recurrent cysts, an implantable reservoir may be inserted to periodically drain the cyst. As craniopharyngiomas grow from within the stalk of the pituitary gland, hormonal imbalances (especially of sodium-water) are commonly seen after treatment. For those tumors that involve the hypothalamus, a syndrome of hyperphagia (excessive appetite) may develop that can lead to obesity. Surgery to remove these tumors may be carried out using a number of different approaches, including craniotomies and expanded endonasal approaches with pituitary transposition. Staged-procedures using multiple approaches may be necessary, as well, depending on the consistency, size and location of the tumor.

A 32-year-old female, who presented with headaches, personality changes and visual loss, was found to have a large suprasellar mass with
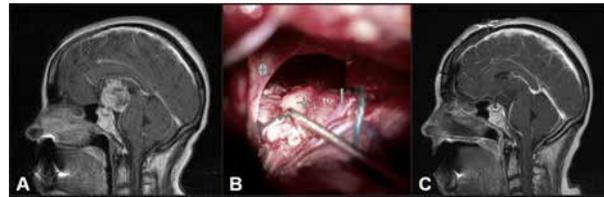

FIGURE 9 | A) Pre-op imaging showing suprasellar retrochiasmatic mass growing into the third ventricle. B) Intraoperative photo showing tumor (star) being resected through opening in lamina terminalis, behind the optic chiasm (crosshair) and medial to the internal carotid artery (arrow). C) Post-op imaging showing complete resection using an bifrontal craniotomy with orbital bar osteotomy.

extension into the hypothalamic and third ventricle with resultant hydrocephalus. She had a solid tumor located primarily in the third ventricle with a pre-fixed optic chiasm, with essentially no space between the tuberculum sellae and the optic chiasm. A bifrontal craniotomy with orbital bar osteotomy was used to perform a translamina terminalis approach to the third ventricle for access to the tumor. Using this corridor, the tumor was completely resected. Her visual function and headaches improved prior to discharge from the hospital. As is commonly the case, she did require early hormonal supplementation and demonstrated early signs of hyperphagia.

Anterior skullbase tumors are a diverse set of pathologies. Tumors of this region may affect the olfactory nerves, the frontal lobes, the visual apparatus, the pituitary gland as well as the critical intracranial vessels the run through this region. Optimal treatment of these diseases requires comprehensive evaluation of these systems and consideration of various surgical approaches using minimally invasive keyhole approaches, stereotactic radiosurgery, endoscopic endonasal approaches and craniotomies. Many of the common tumors that occur in this region are WHO grade I (non-infiltrative) tumors, where complete resection can provide a cure.

The first surgery is the best and safest chance to achieve this. It is critical to have a well-trained and comprehensive team-based approach to treating these tumors, such as is being offered at Palmetto Health-USC Neurosurgery. ◄

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