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Editorial

Ignorantiology, Epistemology, Teleology

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The new millennium is the time of amazing, ever-new techno-possibilities. Advanced Imagery, Accessive, Assessive, and Operative innovations may allow a neurosurgeon to excise a glioma or do a CSF shunt or clip an AVM, robotically, while sitting in his office. Such sophistication and wizardry, alas, has not/cannot provide any insight into the Cause, Course, n, Cure of the basic pathologies, whatsoever. Gilles and Millard have aphorized that from the time that a flint stone slit open an abscess and a horse hair closed a wound, surgery hasn't marched much further. A Washington Congress on Stroke summarized that the management of stroke begins with its diagnosis, and ends there. Some rules govern such an impasse wherein science lags behind and technology leapfrogs all the time.

The science of ignorance, christenable as Ignorantiology, has been knocking the doors of medicine to be made integral to the undergraduate and post-graduate curricula. The pioneering text in this field is The Encyclopedia of Ignorance (Simon n Schuster 1976), a tome by 52 authors, quite a few being

th

century summed up that 'If gyan (knowledge) is infinite, so is agyan (ignorance)'. To this, Pascal gave the 17th century metaphor: Knowledge is the inner surface of a sphere the outer surface of which is painted with ignorance. This more than vindicates Boyd's generalization on diabetes mellitus: The more we know about it, the less we seem to understand it. You could replace, in the foregoing, diabetes mellitus by cancer/stroke/CAD/ arthritis and couldn't go wrong. No element of neuroscience – nerve cell, glia, meninges, vessels – is exempt from this preamptory paradox. Szent-Gyorgi, the Nobel-laureate, chairing a CIBA symposium on Submolecular Biology of Cancer, admitted that he couldn't say what is a cancer cell, because he didn't know what is a normal cell.

Einstein's summing up of the state of human ignorance is tellingly precise. 'If I have learned something from the speculations of long life, then it is this that we are much longer distance away from a deep insight in the elementary processes of Nature than most of the colleagues of our time believe'. His young son once asked him: Daddy, why are you famous? Einstein's reply was innate humility born out of clarity: "You know son, we were a bunch of blind bugs crawling over a sphere. I happened to be the one to make out that the surface is curved". Lyall Watson on the east of the Atlantic, and Lewis Thomas to Atlantic's West, have expressed that the greatest discovery of the 20th century is the profundity of human ignorance.

Epistemology, or gnoseology (from gnan) is the recently evolved science of evaluating the scope-n-limitations of any idea/action. It strives to tell you what you can, and what all you just cannot. As Ardrey put it: With all that science knows about gravity over 250 years, the Newtonian apple won't fall up. Medicine's ever-expanding Knowledge-Niagara on cell fibre, neurone, coronary, carotid or cancer has failed to empower medicos to alter the cause/course/cure of human illnesses by dictating therapeutic terms to the aforelisted elements. Wound-healing, the presiding deity of all surgery, just occurs, no one knows how, be it a shaving scratch or severe polytrauma, or wide-n-deep neurosurgical invasion. Medicine's antimicrobial Eureka post-Domagk n-Fleming, has failed to survive for even 50 years, multiresistant strains being now a common reality. Epistemology teaches that, since the total microbial biomass outweighs the total animal biomass (worm to whale) by a huge margin, and since every

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human is closely covered by 2.2 Kg of microbes, an antimicrobial, no matter which generation of the latest cephalosporin, serves only as a microflorafluctuator, often driving away the beneficial ones that get replaced by the sinister ones. This drives home a Copernicus reversal: Microbes are the tolerant hosts, and we humans, the pampered guests. Abjuring all antimicrobials may prove to be the sanest action, in all clean neuroprocedures, daring to do so even after draining/ excising a brain abscess. Macewen's success rate with brain abscesses at the close of the 19th century, match that of neomillenium.

From Cajal to Eccles has been a long, brilliant journey, that, however, has failed to alter the trans-science and trans-technique aspects of neurosurgical problems. Surgery remains the supreme palliation, but that's where its scope ends. The moral is clear: Palliation can never be preemptive. A disc declaring its prolapse on MRI or an AVM by any means, but with the owner at peace with the so-called manifest pathology, has to be left unmolested. Primum, non nocere. Secundum, quieta non-movere. Remember Hoerr's law: It is impossible to make an asymptomatic person feel better. The immediate and inevitable corollary is: By 'treating' an asymptomatic person, you can convert him into a patient, rendering the situation much worse than before.

Teleology is the brain-child of well-reasoned Ignorantiology, and Epistemiology. Teleology's sense of worship is a psychodynamic sequence of profundity of ignorance spawning admiration begetting sense of wonder leading to philosophy ending in worship; much akin to Einsteinean awe for the mysterious. The vanity-n-conceit of the educated – medicos obviously included – are unlikely to be reverential. In the neuraxial galaxy of neurones and ten-fold neuroglia, a perfect order prevails: Nobelist Burnet eulogizes: "Primitive neurones seem almost to be programmed individually, each to move and direct its axon along an elaborately predetermined course."The path-precision of each dendron and axon allows no revised situational shift and hence disinclination of nerve cells to multiply to heal a neuraxial wound. Neurones, as a tissue, aren't granted tolerance by the thymus, and hence it is better that neurons don't multiply to heal wound lest a neuroprotein leaks to invite thymic wrath to precipitate a so-called auto-immune encephalomyelitis.

The contralaterality of cerebrosomatic control allows Nature to make each crossing fiber to contact its opposite member, establishing thereby a neuraxial commissure greater in bulk than all the commissures, including the corpus callosum, lumped together. The brain, weighing as much as the liver, avoids its burden on the dural venous sinuses on the floor of the skull by the almost weightlessness that it achieves by floating aloft in isodense neuraqua (CSF). Hans Kreb, the Nobelist for the Urea Cycle, underscores the value of teleology by quoting the great physiologist Ernst von Brucke: "Teleology is a lady without whom no biologist can live. Yet he is ashamed to show himself with her in public".

Teleology is no whore or a call-girl, but an integral part of any science more so neuroscience, replete as it is with one unfathomable mystery after another. It's time to adopt into neurological thinking and doing, the Holy triad of Ignornatiology, Epistemiology and Teleology. This done, the poetry of the intellect will non-divorceably get wedded to the prose of neurosurgical practice.

Aspergillus infection of the Central Nervous System

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Abstract

Aspergillus fumigatus is the most common human pathogen in the genus Aspergillus. Intracranial granulomas, abscesses, and blood vessel invasion are characteristic features of aspergillosis. Presenting features are those of focal neurologic deficits due to intracranial mass lesions. Paranasal sinus or repiratory tract fungal infection is usually concomitant. Aggressive surgical excision combined with systemic antifungal therapy is the mainstay of treatment. Liposomal preparation of amphotericin B offers better penetration of the drug with reduced side effects. The prognosis for central nervous system aspergillosis is poor and the disease is usually fatal.

Key words: Aspergilloma, brain, fungi, amphotericin

Introduction

The word fungus has an interesting etymology, being sfungus = sponge, one with many pores. Homer's Odyssey (1050-850 B.C.) refers to the 'many-pored sponges'. So, porous, sporous, spongous, sfungus, fungus. The white mold on your brown bread is porous and foretells you of the porosity of the bread that is fungal in origin. The science of fungi isn't fungology but mycology, from Gk. mycos = fungus or mushroom. The science of mycology dates back to 1677 when Hooke, a contemporary of Newton and the first to microscopically describe and name a 'cell', discovered that the yellow spots on rose-leaves consisted of filamentous fungi, the study of which he started. Saccardo, in 1906, published an 18-volume Sylloge fungorum, carrying an account of 57,660 fungi, a figure crossing 150,000 as of today. The whole antibiotic era started with the fungus Penicillum notatum that favored Fleming, Florey and Chain with a Nobel prize.

Fungi are common in the environment, but only a few are pathogenic. In general fungi are organisms of low pathogenicity, emerging as opportunistic organisms thriving in a compromised host, however some will infect even normal hosts. Aspergillosis is an infection of tissues or cavities by fungi of the genus Aspergillus. In the nervous system, the infection can be found in the cerebral parenchyma, the meninges or the vascular system.

Fungal infections of the central nervous system (CNS) are almost always a clinical surprise. Their presentation is subtle, often without any diagnostic characteristics, and they are frequently mistaken for tuberculous meningitis, pyogenic abscess, or brain tumor. Granulocytopenia, cellular and humoral mediated immune dysfunction are predisposing factors to the development of CNS infections in immunosuppressed patients. Only with a high index of suspicion, an aggressive approach to diagnosis, and rapid vigorous therapy may we hope to alter the clinical course in this group of patients.[1]

Intracranial fungal infections are being identified more frequently due to the increased incidence of auto-immune deficiency syndrome (AIDS) patients, better radiological investigations, more sensitive microbiological techniques, and better critical care of moribund patients. General awareness of the possibility of fungal infection has also increased.

Disseminated aspergillosis is more common in an an immunocompromised host as an opportunistic infection as seen in acquired immune deficiency syndrome (AIDS). CNS aspergillosis is also seen in cardiac, renal and other organ transplantation patients. It is also

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noted in neutropenia associated with acute leukemia and its therapy, and patients of glioblastoma multiforme on steroid therapy.[1]

The Organism

Aspergillus fumigatus is the most common human pathogen in the genus Aspergillus, but A. flavus, A. niger, and A. oxyzae are also frequently seen. They have worldwide distribution. Aspergillus are saprophytic opportunistic ubiquitous fungi found in soil, plants and grows as a mold on decaying vegetable matter. It has branching septate hyphae varying from 4 to 12 microns in width, which show dichotomous branching and produces numerous spores on the tips of long conidiophores.[2]

Aspergillus fungal spores are commensal in the respiratory tract and external auditory canal. Maxillary sinusitis of dental origin or the lungs are the most common sites of primary Aspergillus infection. The primary portal of entry for Aspergillosis organisms is the respiratory tract. Infection reaches the brain directly from the nasal sinuses via vascular channels or is blood borne from the lungs and gastrointestinal tract. Rarely the infection may also be air borne contaminating the operative field during a neurosurgical procedure.[3] CNS infection has also occurred as a complication of pituitary surgery.[4]

Neuropathology

Intracranial infection spread of Aspergillus infection occurs more frequently through the hematogenous route and less frequently through direct or contiguous spread. Direct extension from the sinuses or orbit has been reported. Dissemination of the Aspergillus fungi to the brain from a pulmonary source occurs in 10% of patients. Direct infiltration into the basal bones leads to the more commonly encountered skull base osteomyelitis. Intracranial infection can affect the parenchyma or the meninges. According to the site and nature of infection, the patient may present with features of meningitis, focal neurological signs or symptoms of raised intracranial pressure. The cerebral vasculature can be involved by mycotic aneurysms or intra-arterial thrombosis. Aspergillus hyphae can invade directly into the vessel wall which becomes weakened due to necrosis and polymorphonuclear infiltration, resulting in mycotic aneurysm formation. These patients may present with typical subarachnoid hemorrhage syndrome. Intraluminal extension of the hyphae can also initiate thrombus formation. Rarely, major arterial stenosis may occur following leptomeningeal infection. Steroids can inhibit the macrophage response to intracellular fungus and may permit enhanced germination.

Single or multiple abscess formation with blood vessel invasion leading to thrombosis is a characteristic feature of Aspergillosis on neuropathologic examination. Aspergillus has a marked tendency to invade arteries and veins (angiotropic) producing a necrotizing angitis, secondary thrombosis, and hemorrhage. Onset of cerebral aspergillosis is heralded by manifestations of focal neurologic deficits in the anterior and middle cerebral arterial distributions. The evolving hemorrhagic infarcts convert into septic infarcts with associated abscesses and cerebritis. The fungal hyphae are found in large, intermediate and small blood vessels with invasion through vascular walls into adjacent tissue; invasion in the reverse direction can also occur. Purulent lesions may be chronic and have a tendency toward fibrosis and granuloma formation. Microscopically the most striking feature is the intensity of the vascular invasion with thrombosis. In purulent lesions, pus is seen in the center of the abscesses with abundant polymorphs at the periphery. Granulomas consist of lymphocytes, plasma cells and fungal hyphae.[5]

Clinical manifestations

Aspergillosis should be considered in cases manifesting with acute onset of focal neurologic deficits resulting from a suspected vascular or space-occupying lesion especially in immunocompromised hosts. In patients with paranasal sinus disease, orbital extension with proptosis, ocular palsies, visual deterioration, and chemosis may occur. The symptoms frequently encountered are headache, vomiting, convulsions, hemiparesis, fever, cranial nerve deficits, paralysis and sensory impairment of varying degree. Features typical of meningitis

and subarachnoid hemorrhage resulting from mycotic aneurysms may manifest.[1,2,5]

Patients are often afebrile or have only a low-grade fever. Their symptoms are usually those of a cerebral mass lesion, although the propensity of the fungus to invade blood vessels may lead to extensive necrosis and sometimes to intracranial bleeding.[6]

The disease is usually slowly progressive and symptoms may persist for months. Brainstem or cerebellar signs were the presenting features in one series of 11 patients, in which rapid neurologic deterioration and death occurred in 9.[1]

Goel et al[7] have reported aspergilloma to involve the Gasserian ganglion in two healthy individuals. These paracavernous tumors mimicked a meningioma and a trigeminal neurinoma on preoperative imaging and intraoperative consistency and vascularity. The lesions were successfully and completely resected. Both patients developed major cerebral arterial territory infarcts in the postoperative phase, remote from the site of the operation, leading to crippling neurological deficits in one patient and death in the other. Nadkarni et al [8] have reported a similar clinical course in a 32-year-old male with paranasal sinus infection with intracranial extension. This patient succumbed to a basilar artery thrombosis following a left frontal granuloma excision (Fig.1). These cases highlight the unusual location of intracranial aspergilloma and the possibility of ischaemic complications after surgical resection of intracranial aspergilloma.

Of the 73 patients treated for fungal infection between 1967 till date in our Institution, 22 patients had a histological confirmation of the diagnosis of CNS aspergillosis. There were 14 males and 8 females in this group and their age ranged from 20 to 58 years (average 44 years). Three patients tested positive for human immunodeficiency virus infection. Four patients had diabetes mellitus. The lesion in four cases was in the proximity of cavernous sinus. In one case, the lesion was within the dural confines of the Meckel's cave and extended in a plexiform manner along the second division of the trigeminal nerve. In another case the extensive basal lesion involved the paranasal sinuses, orbit, cavernous sinus and the medial temporal brain. In rest of the eighteen cases, the lesion was located within the cerebral hemisphere and presented as a large mass with extensive cerebral edema. All 22 patients succumbed to their disease within one year of diagnosis. Autopsy was performed on 14 of these patients as they died during their hospital stay within ten days of surgery. Twelve of these patients harbored aspergillus granulomas with abscesses. The brain showed evidence of meningitis and generalized cerebral edema. The intracranial vasculature in 3 of these patients showed aspergillus invasion and secondary thrombosis. One patient had been operated for cavernous sinus aspergillus granulomas. This patient died postoperatively after developing arteritis and an infarct distal to the site of surgery. Autopsy examination confirmed that fungal arteritis that led to the cerebral infarcts. Another patient had a basilar artery thrombosis and a massive posterior circulation infarction in the post-

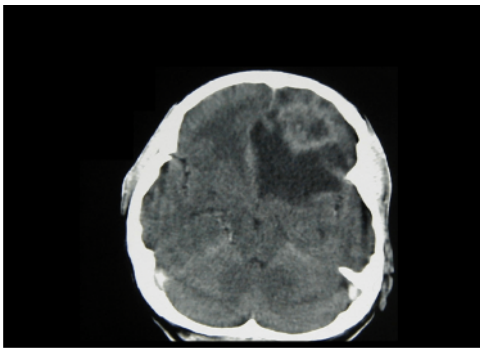

Fig 1A. Post-contrast axial Computed tomography (CT) scan shows a left frontal aspergillus granuloma

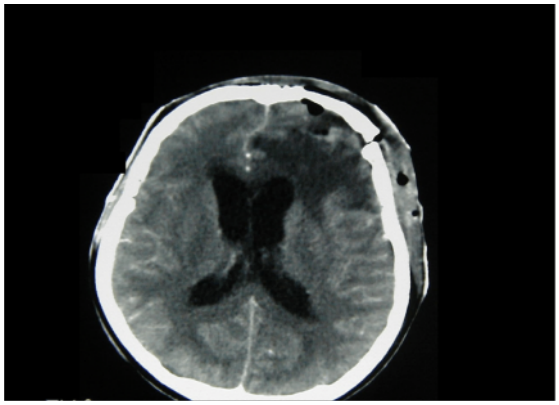

Fig 1B. Postoperative CT scan shows excision of left frontal granuloma by a left frontal craniotomy

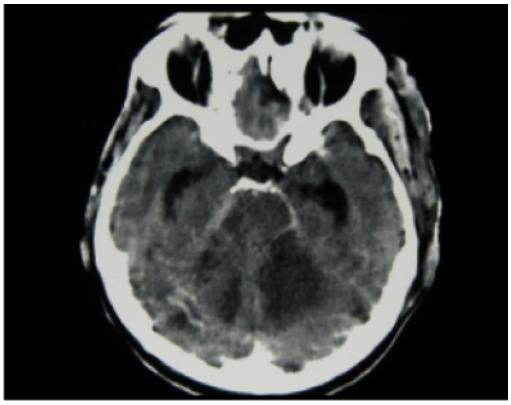

Fig 1C. Postoperative CT scan shows bilateral cerebellar and brainstem infarcts noted as hypointense areas.

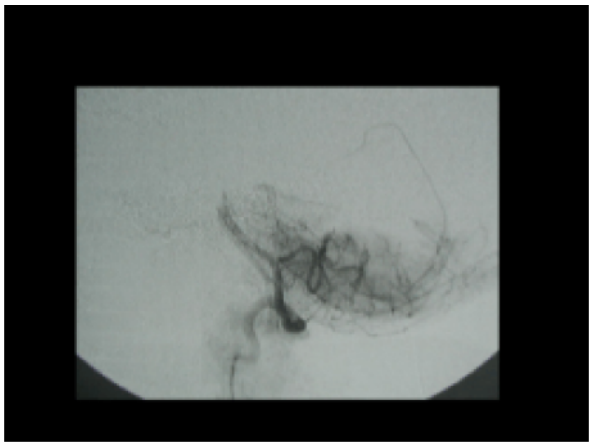

Fig 1D. Vertebral angiogram demonstrates complete occlusion of basilar artery.

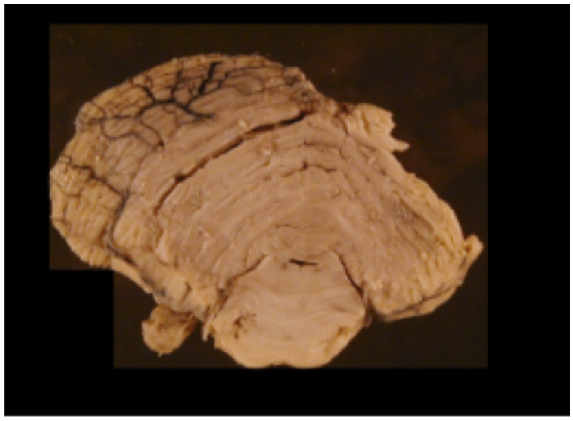

Fig 1E. Axial cut section of the post-mortem specimen of the brain shows a brainstem infarct.

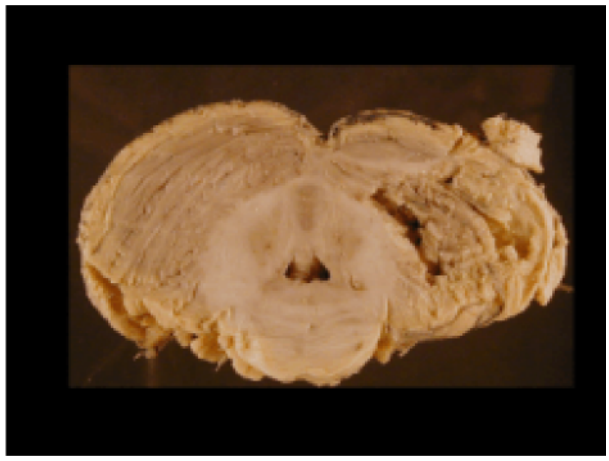

Fig 1F. A section taken inferiorly shows a cerebellar infarct

operative phase(Fig.1) . Autopsy study and examination of the basilar artery confirmed presence of aspergillus fungus within the artery and thrombosis of the vessel.

Investigations

Spinal fluid findings

In general, lumbar puncture is contraindicated in patients with intracranial mass lesions associated cerebral edema. Altering the intracranial pressure by withdrawing spinal fluid for laboratory examination may precipitate a cerebral herniation syndrome or abscess rupture into the ventricular system.

Spinal fluid pleocytosis (600 cells / mm3) and moderately elevated CSF proteins are present, but CSF glucose is usually normal in CNS Aspergillosis. There are many exceptions to this picture and virtually any CSF response can occasionally be seen, including a normal spinal fluid. Organisms are rarely found in CSF. The characteristic branching sepatate hyphae and conidia of Aspergillus species are faintly visible with H & E stain and periodic acid-Schiff (PAS) but are most readily seen with Gomri's methenamine silver (GMS) stains. Potassium hydroxide wet preparations can demonstrate Aspergillus. Red blood cells may be seen in the CSF of patients with CNS aspergillosis.[1,2]

Neuroradiology (Figs.2 and 3)

Diagnosis of an intracranial mass lesion is best confirmed with a computed tomography (CT) or magnetic resonance (MR) imaging of the head with or without intravenous contrast. On CT low density lesions that may or may not enhance with contrast can represent fungal

abscesses. Chronic abscesses have demonstrated ring and homogenous enhancement. Minimal mass effect, low absorption areas, and slight or no contrast enhancement were seen on CT in patients with A fumigatus brain abscess. The increased sensitivity of the MR imaging scan can

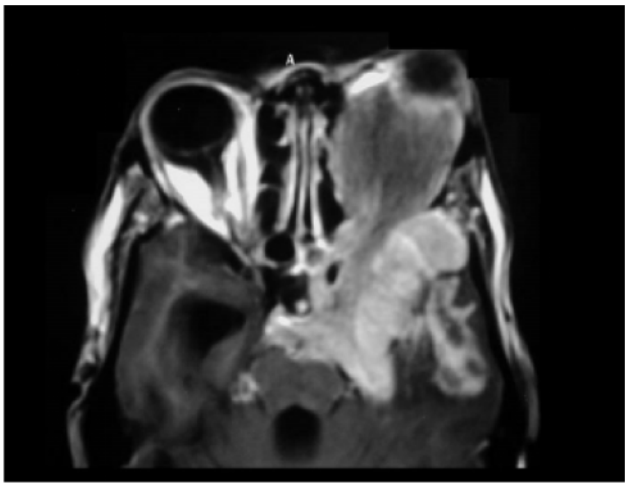

Figure 2A. Post-Gadolinium magnetic resonance (MR) axial image that shows an enhancing mass extending from the orbit into the cranium. The mass invades into the ethmoid sinuses, cavernous sinus, sphenoid sinus, and middle cranial fossa. The internal carotid and basilar arteries are encased in the inflammatory tumor. The temporal brain has been infiltrated.

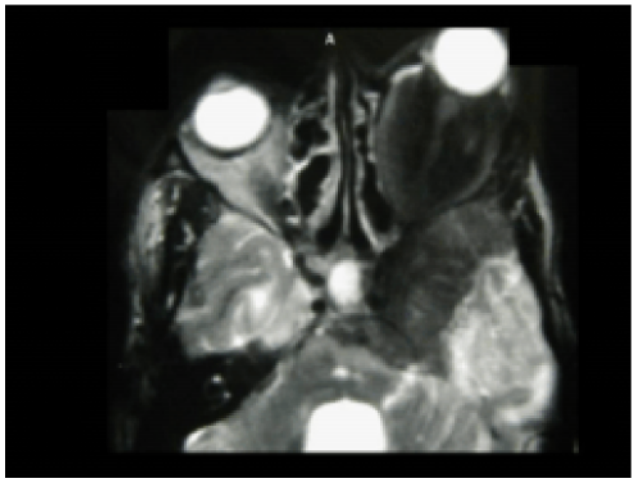

Figure 2 B. T2-weighted axial MR image shows that the mass is hypointense, typical of an inflammatory granuloma. Histologically this tumor was an aspergilloma

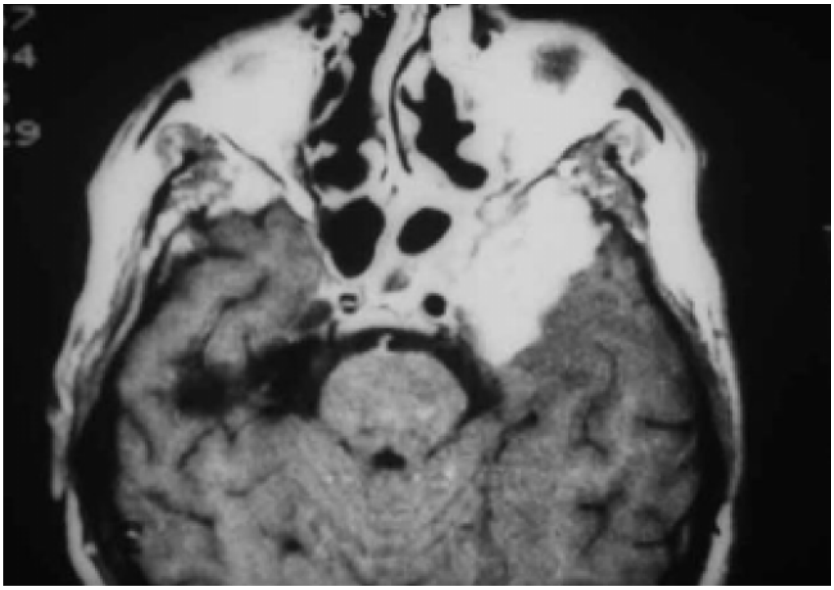

Figure 3 Post-Gadolinium magnetic resonace (MR) axial image shows an enhancing cavernous sinus mass. The mucosa of the sphenoid and ethmoid sinuses are thickened and enhancing. Histology confirmed the mass to be an aspergilloma

be useful for demonstrating multiple small intracerebral abscesses not apparent on CT. CT scanning also provides a convenient way to monitor a patient's response to anti-microbial therapy.

Culture

Aspergillus cultured optimally on Sabourad's agar demonstrates characteristic conidiophores. However, blood and cerebrospinal fluid cultures, even in disseminated disease are frequently negative.

Serologic Tests

Serial serologic tests (i.e. double diffusion counterimmunoelectrophoresis, immunofluorescence, or enzyme-linked immunosorbent assay) significantly help in arriving at a diagnosis. Immunoasssay may detect the disease early but these tests are rarely done. Serologic testing has been unreliable for A. fumigatus, except in leukemia patients followed prospectively.

Therapy

Surgical excision enhances abscess penetration by removal of necrotic debris.

Radical surgical debridement can be curative in aspergillus brain abscess if the extent of resection extends into uninvolved tissue. Lobectomy in patients with a single A fumigatus abscess is an acceptable surgical option when non eloquent areas of the brain are involved. In four of seven patients with cerebral aspergillosis who survived, complete surgical resection of brain abscess was accomplished.[9] Aggressive neurosurgical intervention for surgical removal of Aspergillus abscesses, granulomas, and focally infracted brain; correction of underlying risk factors; amphotericin B combined with flucytosine and treatment of the source of infection should form the mainstay of the management.

The ischaemic complications after surgical resection of intracranial Aspergillomas are well documented. [7,8] The postoperative phase of patients operated for aspergillus infections of the brain is marred by major cerebral arterial territory infarcts remote from the site of infection, leading to crippling neurological deficits and even death. Histological infection has shown fungal hyphae within the wall of the involved arteries. The stress of surgery and the use of steroids to control cerebral edema in the immediate postoperative phase may have been contributory factors in the fungal growth. High awareness of the possibilities of fungal infection on the basis of radiology or operative findings, avoidance of steroids, and early treatment with antifungal agents may help avoid such a vascular insult.

Stereotactic aspiration is the procedure of choice for most brain abscesses, particularly those measuring more than 1.5 cm. Indications for aspiration include to aid in diagnosis, to relieve mass effect, to improve the efficacy of drug treatment, and when systemic therapy appears to be ineffective for a presumed organism. Complete aspiration of an abscess is not necessary and can predispose to hemorrhage into the evacuation cavity. Stereotactic drainage or biopsy and systemic, intraventricular or intraocular administration of amphotericin B has been effective in Aspergillus abscesses.[1]

Amphotericin B has been the mainstay of therapy for the past quarter century. Combination therapy with 5-fluorocytosine has also been recommended.

Rifampin and 5-fluorocytosine may act synergistically with amphotericin B when treating CNS fungal disease. Itraconazole, miconazole and sulfamethoxazole have also been effective. Because of poor penetration into the CSF when given systemically, direct instillation of amphotericin B into an abscess cavity through an indwelling catheter has been advocated.[10] To reduce the toxicity of amphotericin B, liposomal amphotericin B and its combination with lipids have been introduced. Liposomal amphotericin B (Fungisome™) has been demonstrated to be safe and efficacious in treatment of CNS aspergilloma. [11,12,13] This indigenous preparation is significantly cost effective when compared to other similar preparations.

Whenever possible, immunosuppressive therapy should be lowered or discontinued in the compromised host with CNS infection. Unfortunately, rejection is often concomitant with infection, requiring higher doses of

immunosuppressive agents. In patients with cancer, systemic disease is frequently stable because of continuing chemotherapy administration when CNS infection develops.

Prognosis

The prognosis for central nervous system aspergillosis is poor, with most reported cases being fatal. Fungal abscesses in patients with cancer are usually fatal.[14] An aggressive surgical approach in non-immunocompromised patients helped reduce the mortality form 64% to 39%.[15] Intracerebral aspergillosis is frequently fatal in immunocompromised patients, with only 12 reported cases of successful treatment.[10]

Because many immunocompromised patients have had years of productive life before developing CNS infection, rapid diagnosis and effective medical and surgical treatments are essential to preserve neurologic function and assure a good quality of life.

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Trigeminal Neurinomas: A Review of a Personal Series

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Abstract:

The surgical management issues of 157 cases of trigeminal neurinoma treated over a 20-year period were analyzed. The case records and radiologic material of these patients who were operated on in the Neurosurgery Department at King Edward Memorial Hospital and Seth Gordhandas Sunderdas Medical College, Mumbai, between the year 1989 and 2009 were retrospectively analyzed. The appropriateness of the selected surgical route is studied. Apart from the other typical presenting features of trigeminal schwannoma, 12 patients presented with the rarely reported symptom of pathologic laughter. Three approaches were found appropriate to treat these tumors: the infratemporal fossa interdural approach, the lateral and anterior basal subtemporal approach, and the retrosigmoid approach. For tumors extending extracranially, a 'reverse skull base approach' that involved basal temporal craniotomy was used. In 129 (82%) cases, total tumor excision was achieved. Two patients died during the postoperative period. During an average follow-up of 52 months, there has been a recurrence in 5 cases. Radical surgery is associated with an excellent clinical outcome and long-term tumor control. A majority of tumors, even those that are large and multicompartmental, can be removed in a single surgical stage and exposure.

Key Words: gasserian ganglion, retrosigmoid approach, subtemporal approach, trigeminal neurinoma

Trigeminal neurinomas are relatively rare tumors and represent 0.2% of all intracranial tumors. (1–12) Trigeminal neurinomas usually arise from the Schwann cells of the sensory root and can originate in any section of the fifth cranial nerve; correspondingly, a variety of symptoms and signs may develop. Improved surgical outcome and long-term growth control have been uniformly reported after the improvement in diagnosis and understanding of the anatomical intricacies of the tumor and advancement in the skull base operative techniques. (13–21) Jefferson (6) presented a classification scheme for trigeminal schwannomas that categorized these tumors according to location. Three distinct types are: middle fossa type (type A); posterior fossa root type (type B), where the tumor is in front of the brainstem; and dumbbell-shaped type with both middle and posterior fossa components (type C). Less commonly, the tumor has an extracranial extension (type D). (7) Yoshida and Kawase (21) classified the extracranial tumor into infratemporal, orbital, and pterygopalatine fossa components (Table 1). We recently reported a series of 28 cases of trigeminal neurinomas with extracranial extension. (22) There was tumor extension along the ophthalmic division of the nerve in 4 cases, along the maxillary division in 5, and along the mandibular division in 13. In 6 tumors there was diffuse extracranial extension and the exact extracranial division of nerve involvement could not be ascertained. In 10 cases, the tumor had a multicompartmental location – in the posterior fossa, the middle fossa, and the extracranial compartment. The series of trigeminal neurinomas in general and of those having an extracranial extension is the largest personal series published in the literature.

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Anatomical Considerations

After its exit from the medial aspect of middle cerebellar peduncle, the fifth cranial nerve traverses under the tentorium and later over the petrous apex, where it forms the Gasserian ganglion. The Gasserian ganglion then divides

into 3 divisions: the first and second divisions participate in forming the lateral wall of the cavernous sinus, whereas the third division exits from the cranial cavity via the foramen ovale and has a short intracranial course. As the fifth nerve travels over the petrous apex, a dural and arachnoid sheath forming the cave of Meckel covers it. There is a large subarachnoid space over the Gasserian ganglion in the cave of Meckel containing cerebrospinal fluid. Apart from this dural and arachnoid envelope, which is continuous with the corresponding layers in the posterior fossa, the fifth nerve is also covered by the 2 divisions of the middle fossa dura, which divide at the lateral border of the Gasserian ganglion. The inner (cerebral) layer continues as the lateral wall of the Gasserian ganglion and cavernous sinus, whereas the outer layer (osteal layer) continues medially and forms the inferior dural layer of Gasserian ganglion and the medial wall of the cavernous sinus. This sheath of dura is closely approximated but manually separable from the inner dural layers. The dural layers can be easily dissected off the Gasserian ganglion because of the large subarachnoid space. The dural layers merge with sheaths of the divisions of the nerve at the level of the foramen ovale, foramen rotundum, and superior orbital fissure, where the dissection of the dura from the neural tissue is relatively difficult. Despite the merging of the meninges, they continue along with the extracranial part of the nerve and are then labeled as perineurium. The superior petrosal sinus traverses in the layers of the dura superior, and the inferior petrosal sinus traverses inferior to the root of the fifth nerve at its entry in the cave of Meckel. The precavernous segment of the carotid artery is posteromedial in relation to the Gasserian ganglion; in approximately two thirds of cases, there is either only a thin shell of bone or a tough cartilaginous layer in addition to the meningeal cover of the nerves that provides a barrier between the carotid artery and the Gasserian ganglion. No matter how big the tumor becomes, it seldom actually pierces the dura and enters into the venous spaces of the cavernous sinus or engulfs the internal carotid artery in its precavernous or cavernous sinus segment. The middle fossa dura was not pierced by the tumors in any of our cases, despite the large size of the tumors. The origin of these tumors is from a segment of the nerve, and rest of the nerve is involved by displacement as a result of the growing mass. From our experience, we believe that the site of origin of these tumors is at the point where the nerve enters the cave of Meckel. Most trigeminal neurinomas, irrespective of the site of spread, have an association with this region of the nerve. The tumor grows larger and spreads in the available space.

The cave of Meckel can accommodate a large amount of the tumor, which enlarges the cave. The tumor presses the adjacent normal fifth nerve, most of which is clinically involved by direct pressure of the tumor. In the posterior fossa, trigeminal neurinomas are located intradurally. However, we have recently identified a number of posterior fossa tumors that are located entirely within the dural confines and not extending into the subarachnoid space. The presence of dura/ meninges around the tumor provides a protective barrier during the operative procedure that assists dissection from closely related cranial nerves and carotid artery (Fig.1). In general, these tumors involve the adjoining cranial nerves, blood vessels, and brain only by displacement and not by invasion. We analyzed 157 cases of trigeminal neurinoma treated surgically during the period from 1989 to 2009 (Tables 2–4).

TABLE 1. Physical characteristics of the tumor

Tumor characteristics	Number of patients	Percentage
Location of tumor		
Type A	57	36.3
Type B	14	08.9
Type C	58	36.9
Type D	28	17.9
Tumor size		
<2 cm	11	06.9
2–4 cm	57	36.9
4–6 cm	69	43.8
>6 cm	20	12.3
Nature of tumor		
Predominantly solid	24	32.8
Predominantly cystic	13	17.8
Mixed	26	35.7
Calcification	04	05.5

TABLE 2. Demographics

Clinical features	Number of patients	Percentage
Age		
0–10 years	04	02.5
11–20 years	34	21.7
21–30 years	43	27.3
31–40 years	36	22.9
41–50 years	23	14.7
>50 years	17	10.9
Sex		
Male	66	42
Female	91	58

TABLE 3. Clinical presentation

Duration of symptoms		
<1 month	19	12.1
1–6 months	74	47.1
6 months–1 year	41	26.1
1–2 years	14	8.9
>2 years	09	5.7
Presenting symptoms		
Facial numbness	121	77
Facial pain	18	11.4
Headaches	107	68.2
Gait disturbance	67	42.6
Pathologic laughter	12	7.6
Hearing deterioration	29	18.4
Diplopia	32	20.3
Visual deterioration	21	13.3
Proptosis	12	7.6
Limb weakness	9	5.7
Seizures	5	3.2

TABLE 4. Physical abnormalities

Cranial nerve involvement	Number of patients	Percentage
Trigeminal nerve		
Sensory		
V1	80	50.9
V2	136	86.6
V3	84	53.5
Motor	131	83.3
Abducens	23	14.6
Occulomotor	9	5.7
Facial	16	10.1
Hearing	24	15.2
Lower cranial nerves	11	7.0
Cerebellar signs	54	34.3
Pyramidal signs	14	8.9

Figure 1a: Line drawing showing the trigeminal nerve and its relationship.

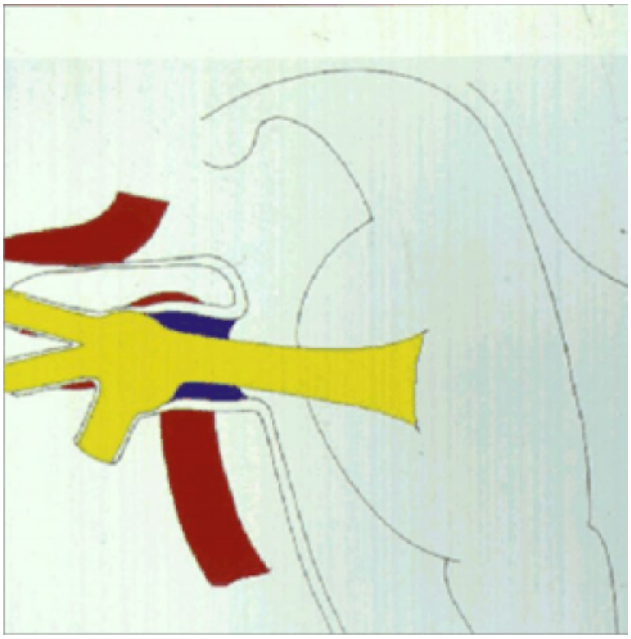


Figure 1b: Dumbbell-shaped trigeminal neurinoma. It is interdural in the cave of Meckel and intradural in the posterior fossa.

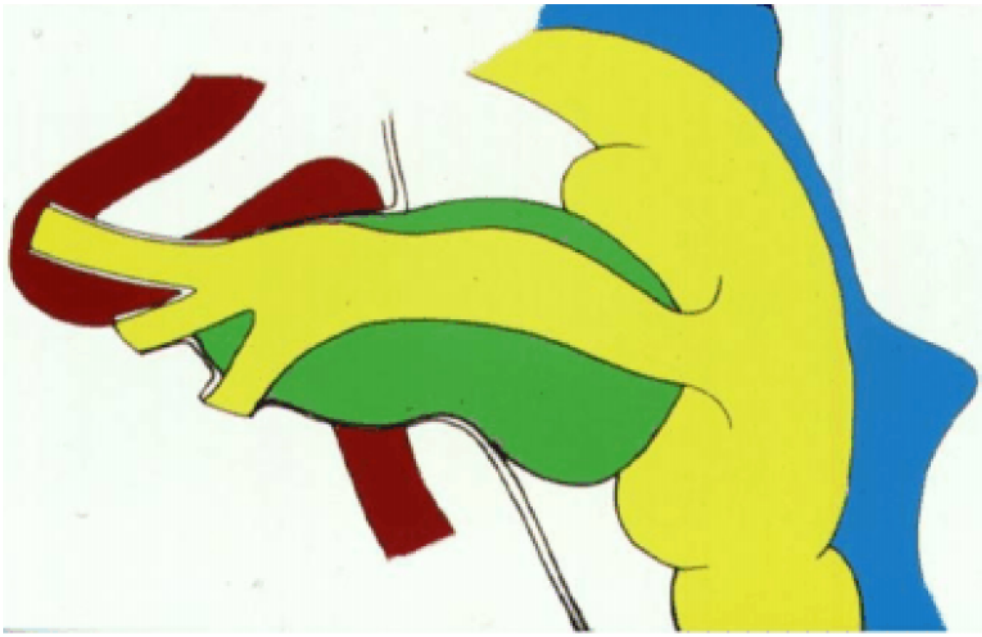
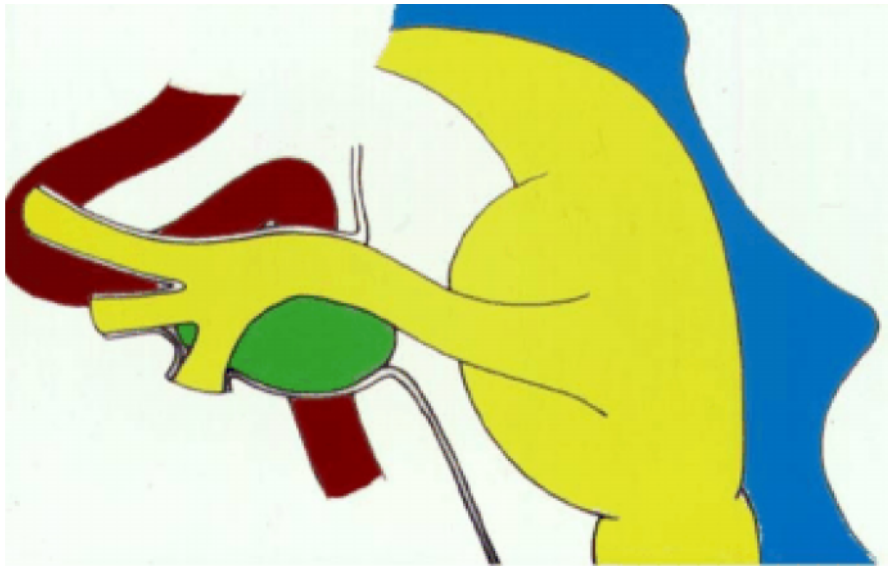


Figure 1c: Line drawing showing a relatively small sized tumor located in the middle fossa.



Clinical Presentation

Table 2 shows the presenting clinical features. There was no significant sex variation in our series, with the male-to-female ratio being 1:1.4. The age of presentation varied from 6 months to 72 years. The age at the time of presentation of 6 months is the youngest in the literature and was reported by us earlier. (23) Neurofibromatosis is less commonly associated with trigeminal neurinomas. (20, 24–27). In our series, 14 patients had features suggestive of neurofibromatosis. Because of the subtle nature of symptoms extending over long periods of time and neglect of early symptoms, probably as a result of illiteracy and ignorance in some of our cases, the majority of the tumors achieved a large size before being diagnosed. The clinical presentation was commonly in the form of paresthesiae or numbness, usually in more than 1 division of the nerve. Severe or neuralgic pain is uncommon and was seen in 9 cases. Wasting of the temporalis and pterygoids was frequent

in 83.3% cases; when present, it was usually diagnostic.

The corneal reflex was depressed or absent in 80 (51%) patients. Dense motor and sensory involvement, including complete absence of corneal sensation, is uncommon and often suggests malignant change in the tumor. Although symptoms of involvement of adjoining cranial nerves in the cavernous sinus and cerebellopontine angle have been reported frequently in the literature, they formed a predominant group, probably because of the large size of the tumors encountered in this series. Twelve patients presented with the rarely encountered symptom of proptosis. The unusual symptom of pathologic laughter was seen in 12 cases of large and dumbbell shaped tumors. (28) Although the exact physiologic cause of the pathologic laughter remains to be defined, on the basis of a literature survey, it seems that the complex combination of extra-axial displacement of the brainstem and medial temporal lobe structures could result in this symptom. It appears that pathologic laughter is an important and possibly early presenting symptom in cases of massive trigeminal schwannoma. The clinical features of slow progressive symptoms and the predominant presence of trigeminal nerve–related symptoms of numbness and wasting of muscles are usually diagnostic. In 5 cases, there was difficulty in mastication that was related to presence of lump in the mouth.

Radiologic Features

The size of the tumors in our series ranged from 8 mm to 7.8 cm (Fig. 2). The physical characteristics of the tumors are shown in Table 3. Bilateral trigeminal neurinomas have only rarely been reported. (27) In this series, there were 6 bilateral trigeminal neurinomas, all associated with features of neurofibromatosis. The contralateral tumor in cases with bilateral trigeminal schwannomas was nonsymptomatic in all cases (Fig. 3). Tumors limited to the middle fossa and dumbbell-shaped tumors occupying both the middle fossa and posterior fossa were more common than tumors located only in the posterior fossa. All tumors with extension into the extracranial compartment had a middle fossa component. Tumors extending into the orbit were seen in 4 cases, extension along the maxillary division of the nerve was seen in 5 cases, and extension along the mandibular division in 13 cases. In 6 cases the tumor was identified in the infratemporal / pterygopalatine fossae, but the exact division of the nerve of origin could not be clearly identified. In two cases the tumor extended into the orbit and probably arose from the lacrimal division of the fifth cranial nerve (Fig. 4). (29) The usual form of trigeminal neurinoma was relatively soft and moderately vascular. The predominant presence of cystic changes was seen in a number of tumors, and there were multiple cysts in 16 tumors. The presence of multiple cysts, although rarely seen in acoustic schwannomas, (30) has never been reported with trigeminal schwannomas. Fluid-fluid level within the tumor cysts was encountered in 8 cases. (Fig. 5) Calcification in trigeminal schwannoma has never been reported but was encountered in 6 tumors. The erosion of the petrous apex and smooth circumferential erosion of the foramen ovale, rotundum and superior orbital fissure on plain radiography or computerized tomography was uniformly observed in larger tumors, and these findings were of diagnostic significance. Although there have been reports of malignant trigeminal schwannomas, (6, 26, 31–34) none of the patients in our series had a malignant schwannoma. Transgression of the medial dural wall and actual invasion into the venous spaces of the cavernous sinus or encasement of the precavernous sinus and cavernous sinus–related internal carotid artery was not encountered in any case in our series but has been reported earlier. (8, 35, 36) The displacement of the internal carotid artery was characteristic and had important diagnostic value. (37) In the posterior fossa, the tumor was located anterolateral to the pons and, like acoustic neurinoma, was “extraarachnoidal” in nature in majority, but ‘interdural’ in some cases.

Surgical Strategy

Surgery for trigeminal schwannomas has evolved along with the evolution of skull base surgical techniques.(20,38) The anatomy of the tumor and its dural covers, anatomy of the region, and anatomy of various approach routes are now better understood. Trigeminal

Figure 2a: Axial computed tomography showing the large dumbbell- shaped trigeminal schwannoma.

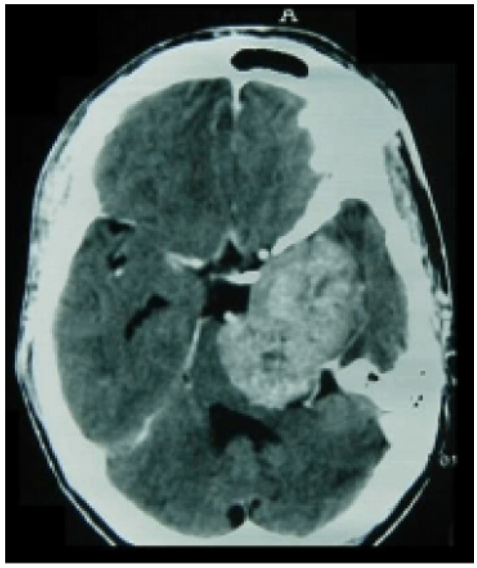


Figure 3: Coronal scan showing bilateral trigeminal neurinoma.

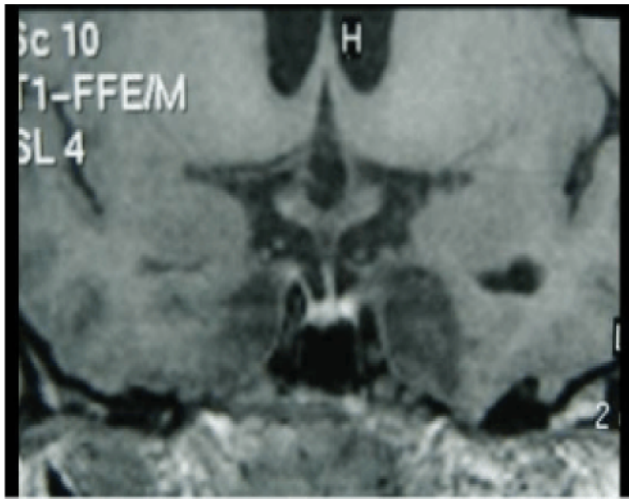


Figure 5a: Axial MRI showing the trigeminal neurinoma. The tumor has cystic necrosis and there are multiple fluid-fluid levels within the tumor.

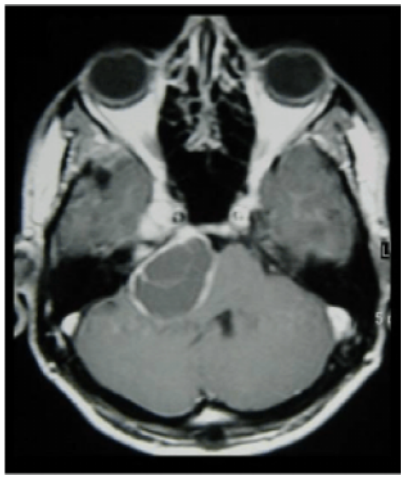


Figure 2b: Postoperative magnetic resonance imaging showing complete excision of the tumor.

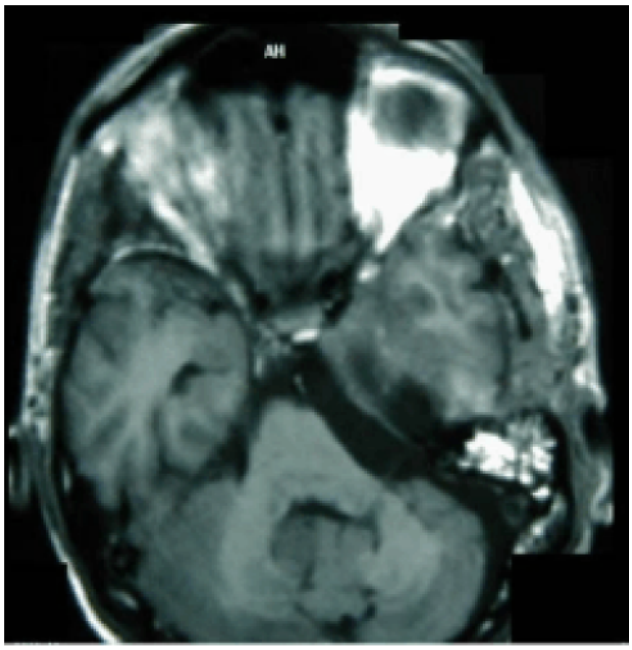


Figure 4: Sagittal T2-weighted magnetic resonance imaging (MRI) showing the hyperintense trigeminal schwannoma extending from the cavernous sinus to the orbital region.

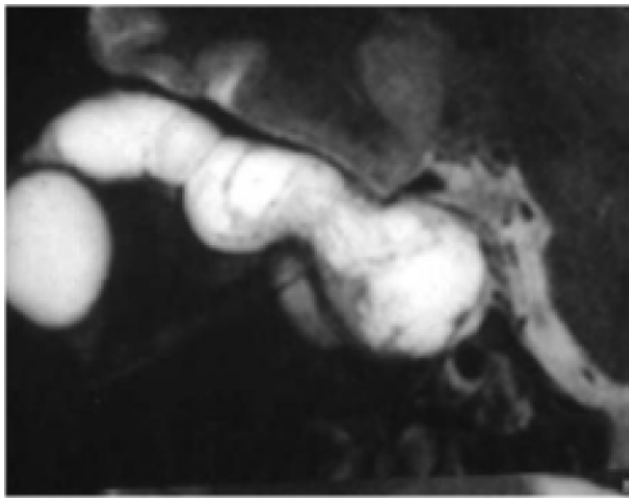
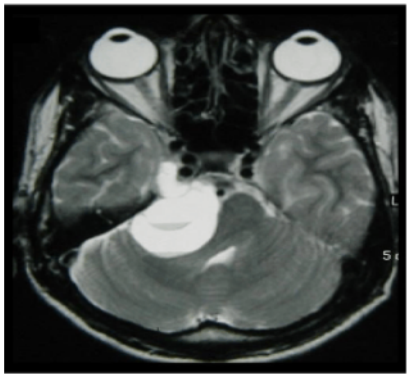


Figure 5b: Axial T2-weighted scan showing the tumor and the multiple fluid-fluid levels vividly.



neurinomas can now be removed by relatively small and straightforward exposures with minimum brain handling.

Various reports have stressed the need for radical surgery, because total resection leads to cure from the tumor and the recurrence rate for cases with partial resection, particularly of cystic tumors, is relatively higher for trigeminal neurinomas than for acoustic neurinomas. (39)

The major impediment to complete removal is an inadequate exposure. Because of their location near the midline and close proximity to vital neural and vascular structures, the ideal surgical approach should be the shortest and most direct; it must be wide and low so as to avoid the need for prolonged brain retraction. It is also necessary that the exposure part of the operation itself does not become unduly time-consuming, tedious, and complex and affect or threaten the anatomical and functional integrity of cranial nerves, major arterial or venous channels, or joints. Toward these objectives, various modifications to the classic approaches have been described.

Even a little extra exposure and working space can sometimes be crucial for radical resection of the tumor as well as for the safety of the patient. The following anatomy and characteristics of trigeminal neurinomas guide the philosophy as regards operative approaches to excise these tumors radically: 1. Trigeminal neurinomas are more frequently soft and suckable tumors. These features make surgery on these lesions relatively easy. Occasional cases of highly vascular and tough tumor may also be encountered. The physical nature of the tumor is more variegated in tumors having an extracranial extension. 2. Trigeminal neurinomas can frequently be diagnosed

on the basis of the presenting clinical and radiologic features. The characteristic location at the petrous apex, dumbbell-shaped appearance, and erosion and widening of the cave of Meckel are frequently seen. The most characteristic feature is the relation between the precavernous and cavernous segments of the carotid artery. Because of the anatomical relation between the carotid artery and the Gasserian ganglion, the precavernous carotid artery is located on the inferior surface of the tumor, whereas the cavernous carotid is displaced medially. 3. Although the carotid artery is in close approximation to the tumor, there is a well-defined dural sheath separating the carotid artery and the tumor. If one remains in the confines of the tumor capsule, there is little danger of injury to the carotid artery. As a result of this anatomical feature, there is seldom any need for perioperative control of the carotid artery. Even the extracranial component of the tumor is surrounded by a relatively tough dural layer that separates it from the adjoining critical neural and vascular structures. 4. Because of its location in the lateral wall of the cavernous sinus, the tumor displaces the venous plexuses and never invades into the venous spaces. If one remains in the tumor capsule, one may seldom encounter venous bleeding. 5. The tumor does not involve all the fibers of the nerve. Some fibers are invariably spared. These fibers can usually be preserved. Working within the confines of the tumor capsule, using blunt dissection with the help of suction or Cavitron ultrasonic aspiratory (CUSA), and avoiding coagulation as much as possible could avoid injury to these fibers. 6. In the posterior fossa, the tumor has a well-defined plane of cleavage from the brainstem, adjoining cranial nerves, and blood vessels. 7. The location of the middle fossa and extracranial components of the tumor is "interdural," whereas the posterior fossa part is "intradural." in majority and 'interdural' in some. This information is useful when dissecting the tumor. A thick dural wall in the middle fossa covers the tumor; hence, dissection is relatively safe in this portion of the tumor. 8. Intratumoral cystic and necrotic changes are common in trigeminal neurinomas, usually making the central part of the tumor soft, and such tumors can be removed with gentle suction or CUSA. 9. Some tumors are firm and fibrous, and some are vascular. Firm tumors can be excised using limited exposure, but the dissection can be relatively difficult in such tumors. One has to restrict the dissection intratumorally and debulk the lesion as much as possible before dissecting the capsule. 10. The retrosigmoid approach is useful for tumors limited to the posterior fossa. Retrosigmoid exposure of the posterior fossa portion of the dumbbell-shaped tumor can be

avoided in most instances. The lateral basal subtemporal approach can provide satisfactory exposure to the entire tumor. 11. A 2-staged approach can generally be avoided. Approaches involving sectioning of the transverse sinus can only be condemned in present-day neurosurgery. 12. Preoperative lumbar drainage of cerebrospinal fluid can be used to great advantage during surgery by means of the lateral basal subtemporal approach. The procedure relaxes the brain and helps by increasing the exposure and protection of the vein of Labbé. 13. Tumors extending into the extracranial compartment can be resected by a 'reverse skull base approach'. The strategy of limited basal temporal craniotomy and retraction of the brain to expose the extracranial component of the tumor can be effectively used for tumor resection.

Operative Approaches

Various operative approaches have been described for the surgical resection of trigeminal neurinomas. (40–42) Skull base techniques have been used to provide for a low and wide exposure and limit the need for brain retraction. This has resulted in a higher percentage of tumor resection, a low surgical morbidity rate, and a lower rate of recurrence. (8, 11, 12, 20, 24, 35, 40) The approaches preferred by the authors are discussed.

Infratemporal Fossa Interdural Approach

Indications

In smaller tumors limited to the middle cranial fossa and where the posterior fossa component of a dumbbellshaped tumor is relatively small, an infratemporal fossa interdural approach can be used (Table 5).

Surgical Technique

The patient is positioned so that the head is extended and turned to the contralateral side. The right-handed surgeon stands on the right side at the level of the chest of the patient irrespective of the side of the lesion and suitably alters the angle of the rotation of the head (Fig. 6). A linear incision is taken over the zygomatic arch, which is completely resected. The temporalis muscle is either split in the direction of the incision or can be reflected superiorly or inferiorly. The muscles of the infratemporal fossa are dissected off the bone by sharp subperiosteal dissection, and the foramen ovale is exposed. With a microdrill, a small craniectomy incorporating the foramen ovale and measuring approximately 3 cm × 3 cm is made in the infratemporal fossa (see Fig. 6). An incision is taken on the lateral surface of the dural sheath of the mandibular nerve at the level of the foramen ovale and extended posteriorly to the inferior and lateral surface of the dural sheaths covering the Gasserian ganglion. The dura over the Gasserian ganglion and the lateral wall of cavernous sinus are reflected, exposing the middle fossa part of the tumor (temporal lobe exposure and a middle fossa floor durotomy are avoided). The bulk of the tumor usually dilates the dural sheaths in each case, and a large exposure can be obtained. After debulking the tumor, the exposure can be further widened. The tumor is followed in the posterior fossa along the cave of Meckel. A large tumor in the region of the Gasserian ganglion is seen to dilate the cave of Meckel, thus providing sufficient exposure to the part anterior to the brainstem. The cavernous sinus part of the tumor can usually be resected by anterior angulation of the microscope. The infratemporal fossa interdural approach uses an infratemporal fossa exposure after sectioning of the zygomatic arch. The association of atrophy of the temporalis and pterygoid muscles with trigeminal neurinomas makes the dissection in the infratemporal fossa relatively easier and the exposure wider. Al-Mefty et al (43) described sectioning of the temporalis muscle at its insertion at the coronoid process and superior displacement of the muscle. The temporalis muscle can also be split in the direction of its fibers or reflected inferiorly and later used for basal reconstruction. (44) The direction of approach and the surgeon's position as regards the patient can be altered to provide direct and low access to the lesion. The route of approach is interdural, avoiding the need to expose the temporal lobe and thus limiting the extent of temporal lobe retraction to the minimum. The possibility of anatomically dissecting the layers of the dura in cases of trigeminal neurinoma has been described earlier. Although the carotid

artery at the petrous apex is not exposed because a dural sheath usually covers it, it is close in the field and can be exposed relatively easily. The tumor bulk widens the cave of Meckel, and a large window can be obtained for the resection of the posterior fossa portion of the tumor. The soft nature of the tumor can be used to circumvent the disadvantage of confronting the tumor before exposure of the brainstem. The approach to the tumor anterior to the brainstem is entirely infratentorial. In our series, the exposure obtained by such an approach was seen to be adequate for safe and complete resection of the tumor. In none of our cases was there any need to extend the exposure for tumor removal. The entire procedure could be performed in a significantly shorter time and was cosmetically appealing.

Figure 6: Line drawing with the surgeon's hands showing the direction of approach. Shaded ipsilateral zygomatic arch and infratemporal fossa bone depict the extent of bone removal for the trigeminal schwannoma shown by oblique lines. The zygomatic arch will be replaced at the end of the operation.

Figure 7: Line drawing showing the scalp incision for the lateral basal subtemporal approach.

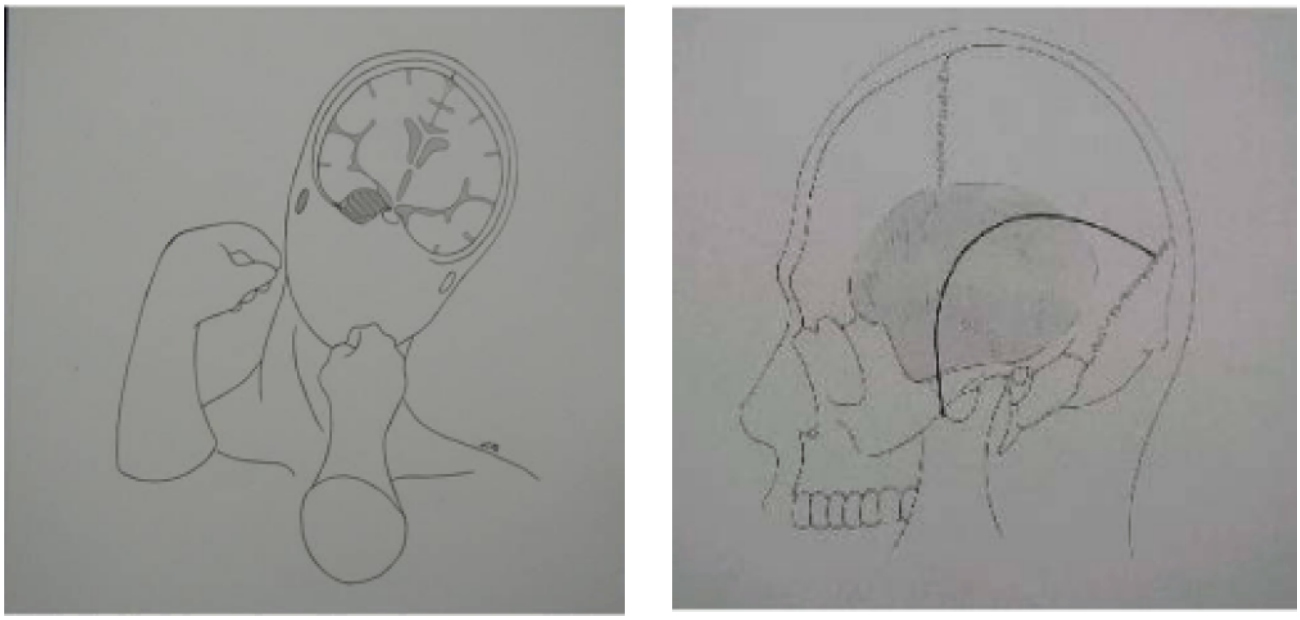
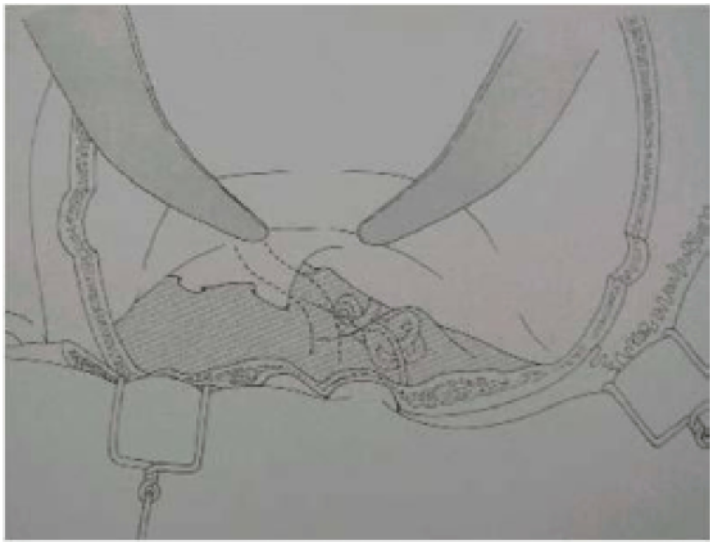


Figure 8: The condyle and superior half of the external canal are unroofed, and the superior third of the mastoid air cells has been drilled to obtain a basal extradural exposure. After elevation of the middle fossa dura, exposure of the foramen spinosum, foramen ovale, foramen rotundum, dura covering the cave of Meckel, and anterior aspect of the petrous bone has been obtained.



Basal Lateral Subtemporal Approach

Indications

For large middle fossa tumors and dumbbell-shaped tumors, a subtemporal craniotomy centered on the external ear canal was found to be suitable to deal with larger tumors located in either or both the middle and posterior cranial fossae. This approach has the advantage of being simple and relatively quick, and general neurosurgeons are familiar with it.

Surgical Technique

The patient is placed in a lateral position. A continuous external drainage of cerebrospinal fluid by lumbar subarachnoid catheter placement is set up. The scalp incision is shown in Figure 7. It starts from a point about 1.5 cm to 2 cm anterior to the tragus of ear and about 1.5 cm inferior to the zygomatic arch. The incision is anterior to the trunk of superficial temporal artery. Working deep to the deep layer of temporalis and masseteric fascia and displacing the soft tissues harboring these tiny nerves anteriorly protect the frontal and zygomatic branches of the facial nerve. The incision curves initially superiorly and then traverses posteriorly. The incision exposes the squamous temporal and posterior parietooccipital bone, posterior third of the temporalis muscle, roots of the zygomatic arch, supramastoid crest, and base of the mastoid process. The incision can be extended further posteriorly and curved inferiorly to enhance the temporal, occipital, and mastoid process exposure. The wide base of the scalp flap and preservation of all feeding arteries ensure its adequate vascularity. The posterior aspect of the temporalis muscle is mobilized in the subperiosteal plane from the temporal bone and from the sharp superior border of the zygomatic arch. The muscle is then rotated anteriorly. A low temporal craniotomy with the base centered on the external ear canal is performed. The anterior and posterior roots of the zygomatic arch, the glenoid fossa, and the lateral half of the roof of the external ear canal are removed in a single piece with the help of a power-driven saw or are resected with the help of rongeurs and a power-driven drill (Fig. 8). Removal in a single piece is frequently difficult and can result in the inadvertent opening up of the external ear canal, a procedure that could affect the sterility of the field. The external ear canal is protected by sharp subperiosteal separation of the canal from the bony roof. The external ear canal has loose fibrous connections to the bony and cartilaginous wall. It is more firmly attached to the spine of Henle, where sharp dissection may be necessary to expose the canal. The meniscus of the temporomandibular joint is exposed but not removed. In tumors limited only to the middle cranial fossa or in smaller lesions, the glenoid fossa may not be removed and mastoidectomy can be avoided. The superior third or half (about 1.5–2 cm below and medial to the supramastoid crest) of the mastoid air cells is drilled. The mastoid antrum may or may not be opened. The drilling of the mastoid process may be continued medially to expose the bony labyrinth around the superior and posterior semicircular canals. The sigmoid sinus and the region of its junction with the transverse sinus are not exposed, and a thin plate of bone is left between the sinus and the mastoid exposure. The dura can now be elevated off the middle fossa floor after sectioning the middle meningeal artery, and a basal extradural exposure is obtained as shown (Fig. 8). An entirely extradural route can remove the tumors limited to or having a larger bulk in the middle fossa after exposing the foramen ovale and dissecting the outer sheath of the dura. In large tumors and those with a significant posterior fossa component, however, an intradural exposure is preferred. By an intradural route and elevation of the temporal lobe, the middle fossa floor and the tentorium are exposed. The bulge of the tumor under the dura of the middle fossa floor is identified. A transverse incision is made over the bulge of the dura, and the tumor within the dural walls is progressively removed, saving the displaced normal trigeminal nerve fibers. An incision is made in the tentorium, which begins at its free edge at the level of posterior end of the cerebral peduncle and is then directed anterolaterally toward the lateral aspect of the superior petrosal sinus. A triangular flap of tentorium is then everted over the superior petrosal sinus, thus providing a wide window from the subtemporal view to the infratentorial structures. By this maneuver, the fourth and fifth

cranial nerve fibers and petrosal vein are protected from inadvertent injury and are exposed widely. The tentorial dural flap is then resected by cutting parallel to the superior petrosal sinus or everted over the middle fossa floor. The posterior fossa component of the trigeminal neurinoma is now exposed. Its consistency, vascularity, and extensions are examined, and the need for further exposure is assessed. Taking an incision exposes the tumor at the petrous apex over the superior dural cover of the cave of Meckel after transecting and packing or clipping the cut ends of the superior petrosal sinus. With angulation of the microscope, the tumor in the lateral dural walls of the cavernous sinus anteriorly and the

cerebellopontine angle posteriorly can be exposed. The entire approach is from the middle cranial fossa. Whenever necessary, expansion of the exposure is possible in various directions. A tumor located in the region of the cave of Meckel and extracranial tumors never transgressed the dural confines, a feature that assisted in developing a plane of dissection of the tumor from the venous spaces of the cavernous sinus and carotid artery and from structures in the infratemporal fossa. Tumor resection is begun from its lateral and inferior aspect in the region of third division of the fifth nerve and then proceeds superiorly, taking special care to avoid injury to the first division of the fifth nerve. After the procedure, the mastoid air cells are packed with bone wax, free muscle, or fat graft. The posterior third of the temporalis muscle along with its fascia can be rotated to the base for strengthening the reconstruction and for providing a vascularized pedicle. If preserved, the bone piece harboring the roots of the zygomatic arch, the glenoid fossa, and the lateral aspect of the roof of the external ear is replaced and sutured along with the craniotomy bone flap. The external auditory meatus is packed with cotton pledget to avoid cicatricial stenosis. The subtemporal or a middle cranial fossa approach has frequently been used for the treatment of vascular lesions and tumors located in the petroclival and clival regions. A common disadvantage of this approach has been damage to the temporal lobe caused by retraction, particularly when the venous drainage is interrupted. The more commonly used methods of basal expansion of a low temporal craniotomy to reduce retraction-related brain injury include a zygomatic osteotomy and inferior mobilization of the temporalis muscle and resection of the middle fossa floor. Partial unroofing of the external ear canal and inferior mobilization or resection of the condyle of the temporomandibular joint have also been recommended for enhancing the inferior angle of vision. A modified basal extension of the lateral subtemporal approach includes resection of the root of the zygomatic arch, roof of the external ear canal, and superior third of the mastoid bone. The inclusion of a mastoidectomy in the exposure adds to the advantages of the more popularly employed petrosal approach to these tumors. The basal extension of the conventional subtemporal or middle fossa approach is frequently carried out by means of a zygomatic osteotomy, which facilitates the inferior displacement of the temporalis muscle. Some reports indicate the usefulness of resection of the middle fossa floor. Such approaches are anterior subtemporal, however, and the working angle to the petrous apex is about 40° to 60° from the horizontal plane in the line of the external ear canal. The posterior subtemporal approach is performed after a mastoidectomy, usually in combination with a presigmoid approach. In such a posterior subtemporal approach, the vein of Labbé obstructs the exposure. A direct lateral approach in the line of the external ear canal, which is almost transversely oriented, is the shortest route to the petrous apex. A basal subtemporal approach has the advantage of ease of working in both the middle fossa and infratentorial compartment and is suitable for all varieties of trigeminal neurinomas. The technique of basal extension of the temporal craniotomy improves the horizontally wide exposure directly in line with the petrous apex. It does not affect hearing or involve facial nerve exposure or manipulation. The function of the temporomandibular joint is not affected, and because there is no manipulation or displacement of the condyle. there is no postoperative pain during mastication. Because the bone in the lateral aspect of the subtemporal route is removed, the operating distance to the

tumor is reduced by about 1.5 cm to 2 cm. Additional inferior and posterior space of about 1.5 cm to 2 cm is also available after a mastoidectomy and removal of the roof of the external ear canal and glenoid fossa. The external ear canal and the condyle and meniscus can be gently depressed inferiorly for this purpose whenever necessary. This space and the relaxation of the temporal lobe after drainage of cerebrospinal fluid provide sufficient exposure for manipulation of instruments and safe dissection of tissues under direct vision and a suitable angle. None of our patients developed any retraction related temporal lobe damage. For the middle fossa component, the inferolateral operative route was found to be considerably safer for preservation of the first division of the fifth nerve than an anterolateral trajectory available by means of a frontotemporal approach. The lateral route also seemed to be safer for the dissection of the tumor from the brainstem because it could be done under vision. The other advantage of the described approach is that it is technically relatively easy. There is no need to expose the superior bend of the sigmoid sinus, which is posterior in the line of the operative direction. The elaborate exposure necessary for mobilization of the sigmoid sinus (as is necessary in the petrosal approach) is avoided. This makes the exposure significantly quicker and safer. The temporalis muscle is displaced anteriorly and thus away from the operative field, and resectioning of the entire zygomatic arch for this purpose is unnecessary. Anterior, posterior, medial, and inferior expansion of the initial exposure is relatively easy. Reconstruction of the exposure is easy and compact and can be done with the help of vascularized pedicled temporalis muscle–based flaps. With the advantages listed here, a basal lateral subtemporal approach appears to be useful for the exposure of trigeminal neurinomas. An additional partial mastoidectomy enhances the scope of the basal subtemporal approach. The ease of expansion of the exposure before or during tumor resection provides versatility to the approach.

However, basal extension of the temporal craniotomy was found to be not necessary in the several cases done in the later part of the series. For over 6 years, basal extension of the temporal craniotomy was not done for resection of a trigeminal neurinoma, irrespective of their size.

For tumors located in the middle fossa and those that are relatively small in size, an anterior temporal basal exposure is useful and basal extension of the temporal craniotomy is not necessary. Extradural exposure from an anterior perspective is easier than an inferior perspective. The tumor resection should however be initiated in the inferior aspect of the tumor to avoid injury to the first division of trigeminal nerve.

For tumors having an extracranial extension, a basal temporal craniotomy was done to expose the extracranial component of the tumor. The temporal brain was retracted to provide an enhanced angle of vision. Retraction of the brain to expose the extracranial portion of the tumor was labeled as ‘reverse skull base’ approach. Whenever necessary, in addition to basal temporal craniotomy, zygomatic osteotomy can be done.

Summary of our Surgical Experience

In the early part of the series, a frontotemporal pterional approach with or without an orbitozygomatic osteotomy and petrosal approaches were employed, but in the later part of the series, these approaches were not used. The main operative approaches preferred and used after the period from 1992 through 2009 to resect these tumors were the infratemporal fossa interdural approach,(39) lateral basal subtemporal approach, (45) , anterior basal subtemporal approach and retrosigmoid approach. The operative approaches and outcomes after surgery are shown in Table 4. A sitting position was adopted for the retrosigmoid approach, whereas the remaining patients were operated on in a lateral position.

Lumbar cerebrospinal fluid drainage was done during surgery in the lateral position. In 7 cases, the operation was done in 2 stages, comprising either the frontotemporal or lateral basal subtemporal approach and the retrosigmoid approach. In the later part of the series, all tumors were removed in a single stage and all dumbbellshaped tumors were resected

by means of the lateral basal subtemporal approach (Figs. 9 - 17). The principal operative finding was that the part of the tumor located in the middle fossa was always confined within the dural walls of the cave of Meckel. Transgression of the medial dural wall and invasion into the venous spaces of the cavernous sinus or encasement of the precavernous or cavernous carotid artery were not seen in any case. In the posterior fossa, the basilar artery and its branches and the adjoining cranial nerves were displaced and never encased by the tumor (Figs. 10, 11). Although most tumors were soft, necrotic, and relatively avascular, some were firm and fibrous and some were vascular. Firm tumors could also be excised using a limited exposure, but the dissection was relatively difficult in such tumors. All tumors were well encapsulated. Even in the extracranial compartment, the tumors were well defined and had a thin capsule, which was continuous with the dura in the region of the cave of Meckel (Figs. 18-20). An attempt was made in all cases to restrict the dissection within the mass of the tumor and to debulk the lesion as much as possible before dissecting the capsule. On the basis of the presenting clinical features and characteristic radiologic signs, a diagnosis of trigeminal neurinoma could be made in the majority of cases. Such a diagnosis was crucially important in planning the surgical strategy for the cavernous sinus–related lesion. The relation between the dura and adjoining structures, which is characteristic in trigeminal neurinomas, may not exist for other tumors in the location.

Total tumor resection was achieved in 129 (82%) cases. More than 5% of tumor residue was not left behind in any case. All these patients in whom subtotal excision was achieved were operated on in the early part of the series. Seven patients underwent a 2-stage surgery, which included a combination of a retrosigmoid approach and a subtemporal approach. In the later part of our series (over the last 9 years), total excision was achieved in the majority of cases; when a “near-total excision” was done, only small residual tumor was left behind. We believe that these improved surgical results of resection in the later part of our series are the result of surgical experience, better imaging facilities, and the addition of skull base techniques. During surgery, the fourth cranial nerve was inadvertently cut in 2 patients, the ipsilateral sixth nerve was damaged in 1 patient, and the facial and eighth nerve complex were damaged in 2 patients. Two patients died in the postoperative period. One of these patients died on the first postoperative day. Postmortem examination showed brainstem infarction. One patient died suddenly on the fifth postoperative day even though he was doing well in the immediate postoperative period and the postoperative scan had shown complete tumor resection. Postmortem examination was not done in this case. Among the complications, cerebrospinal fluid leak from the wound was encountered in 1 case and was treated by lumbar drainage of cerebrospinal fluid. One patient developed an acute extradural hematoma that required emergency evacuation. Postoperative meningitis was seen in 1 case and was treated uneventfully with antibiotics. Osteomyelitis of the bone flap requiring bone flap excision was seen in 1 case. Histologic examination of all tumors showed a benign appearance containing both Antoni type A and B tissue. After surgery, 2 patients developed additional sixth nerve paresis and 2 patients had worsened facial weakness and hearing and developed facial palsy and deafness. Sixth and eighth nerve function did not recover, whereas facial function improved significantly but incompletely on follow- up in both patients. One patient (who developed a postoperative sixth nerve deficit) developed keratitis and permanent corneal opacity 2 months after the surgery. There was no other major morbidity in the series. All patients with preoperative facial numbness remained with some degree of trigeminal hypesthesia. Facial sensation subjectively improved after surgery in majority of patients; however, it was not possible to quantitatively ascertain this fact. No patient with preoperative normal facial sensation developed numbness in the face. Thirteen patients worsened in sensation over the face and developed complete anesthesia in 1 or more divisions of the fifth nerve. Majority of patients had at least subjective improvement in the power of the temporalis and masseter muscles. Wasting of the muscle did not improve in any case. All 12 patients with pathologic

laughter were relieved of this symptom immediately after surgery. On follow-up ranging from 6 months to 19 years (with the average being 52 months), all surviving patients have shown improvement in their preoperative symptoms and functional ability, have resumed their occupation, and are independent. There was a nonsymptomatic recurrence in the region of the cavernous sinus 8 years after surgery in a patient with a massive dumbbell-shaped multicystic tumor. The recurrence is being clinically and radiologically observed. Four cases having extracranial extension had recurrence. Two of these patients were reoperated. Of the cases with bilateral tumors, only the symptomatic tumor on 1 side was treated surgically. No tumor growth has been observed on the nonoperated side during the follow-up period in any case. We found that cystic tumors operated on earlier by only cyst evacuation and small resectioning of the tumor capsule were more prone to recurrence.

Huang (46) evaluated the role of stereotactic radiosurgery for trigeminal neurinomas. He found it to be an alternative primary or adjuvant strategy that controlled tumor growth, did not

Figure 9a: T2-weighted image of an 18 year old boy showing a large dumbbell shaped trigeminal neurinoma.

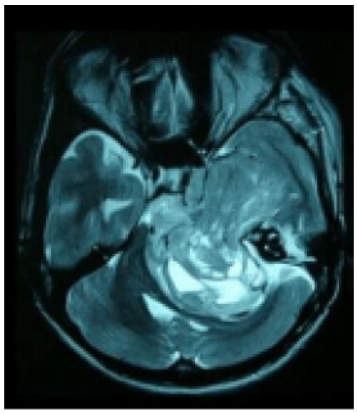


Figure 9b: Sagittal image showing the extracranial extension of the tumor.

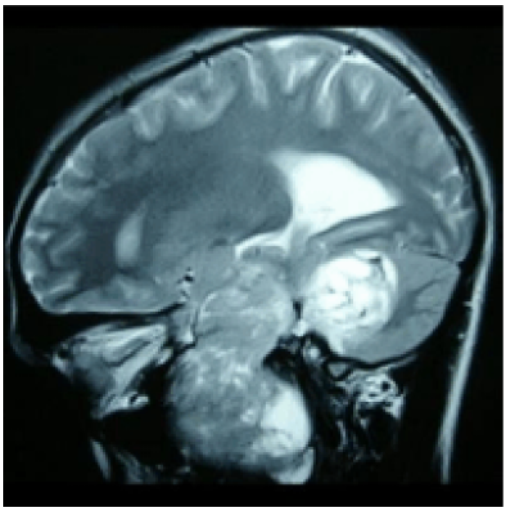


Figure 9c: Coronal image showing the multi-compartmental nature of the tumor.

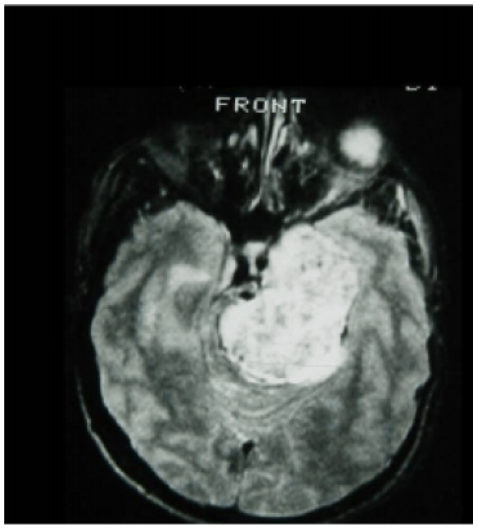


Figure 10a: MRI showing the large dumbbell shaped tumor.

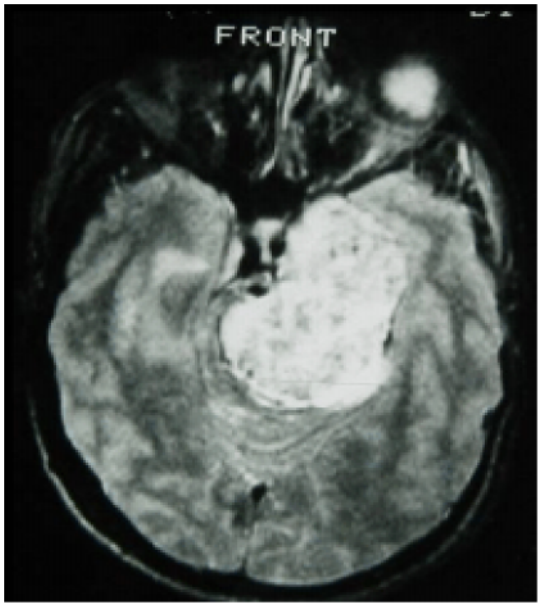


Figure 10b: T1-weighted image showing the tumor.

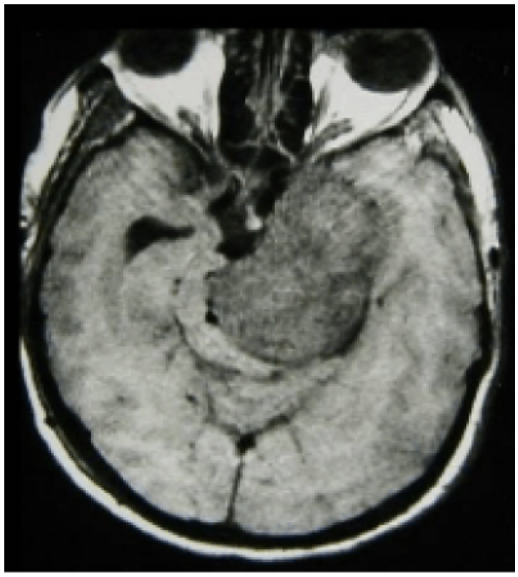


Figure 10c: Sagittal scan showing the extensions of the tumor.

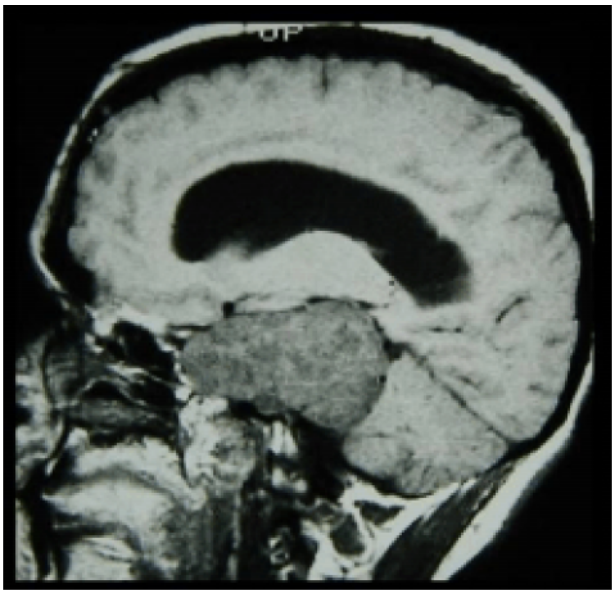


Figure 10d: Postoperative scan showing the tumor resection. The resection was done in two stages.

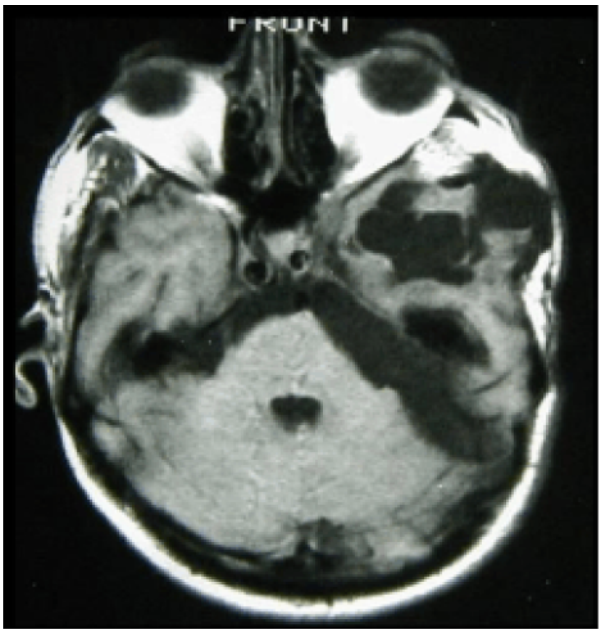


Figure 11a: Sagittal T1-weighted MRI showing the large multi-compartmental tumor in a 36-year old female patient.

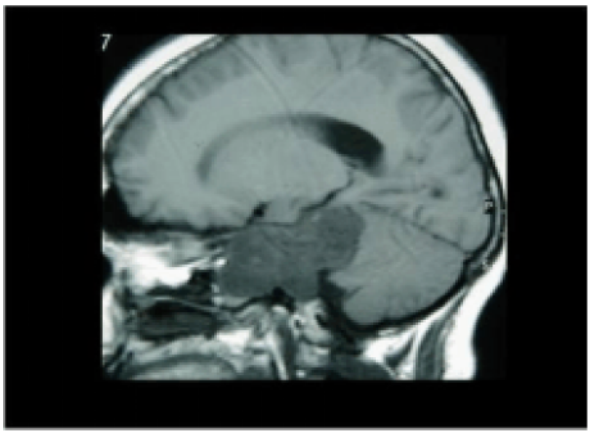


Figure 11b: Coronal image showing the tumor.

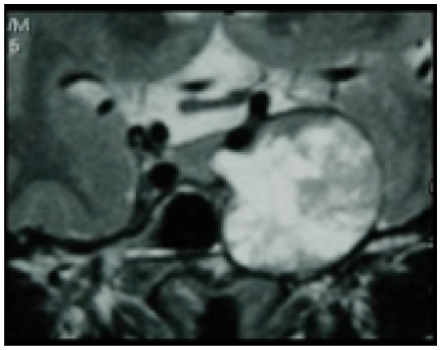


Figure 11c: postoperative scan showing the tumor resection.

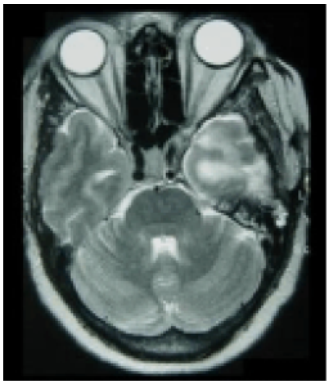


Figure 11d: Coronal scan showing the tumor resection.

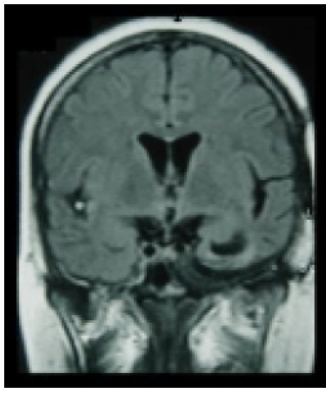


Figure 12b: T1-weighted MRI showing the tumor.

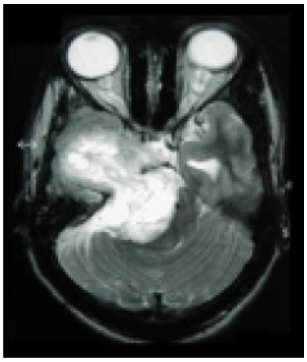


Figure 12d: T2-weighted scan showing the tumor resection

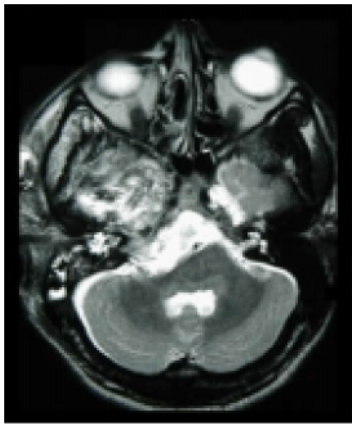


Figure 12a: Axial T1-weighted MRI showing the large dumbbell shaped tumor.

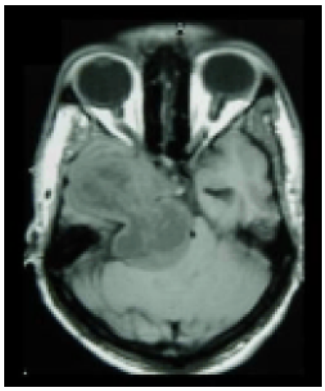


Figure 12c: T1-weighted postoperative scan showing the tumor resection.

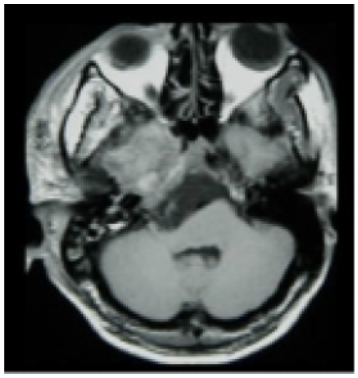


Figure 13a: Axial T1-weighted magnetic resonance imaging (MRI) showing the large dumb-bell shaped tumer.

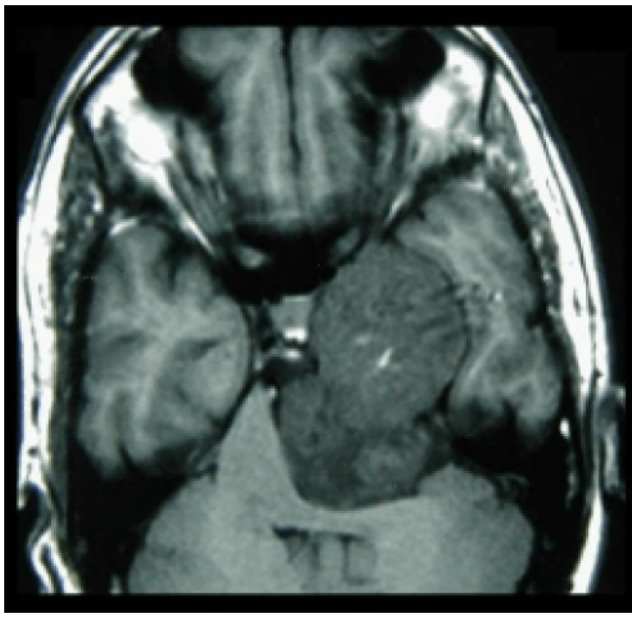


Figure 13b: Axial contrast-enhanced MRI showing the intense enhancement of the dumbbell-shaped trigeminal schwannoma.

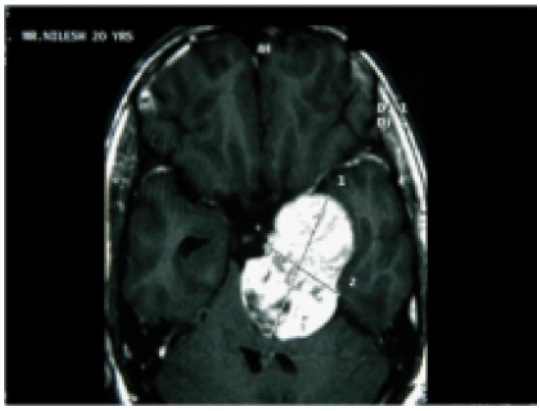


Figure 13c: Coronal image showing the intensely enhancing tumor.

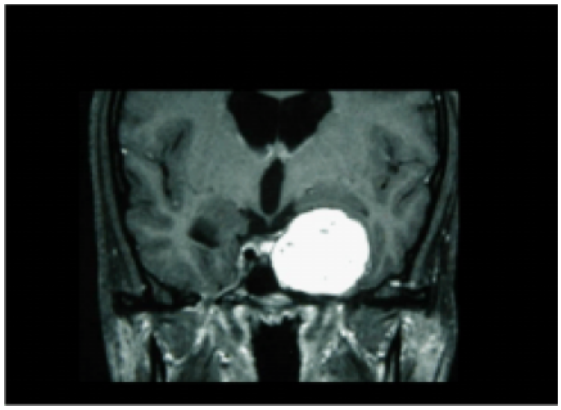


Figure 13d: Postoperative T2-weighted MRI showing complete excision of the tumor.

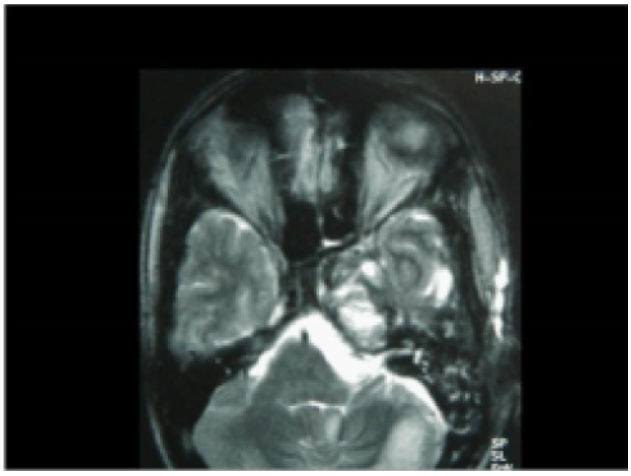


Figure 14a: Axial T1-weighted magnetic resonance imaging (MRI) showing the large predominantly trigeminal schwannoma extending into the orbit, sella, and middle fossa.

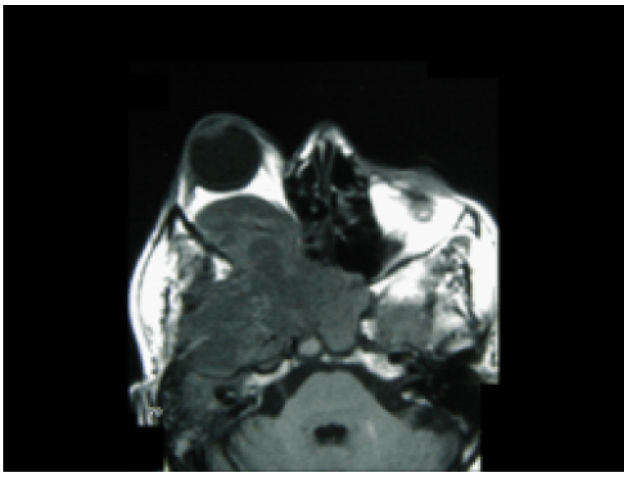


Figure 14b: Axial T2-weighted MRI showing multiple hyperintense cystic areas within the tumor.

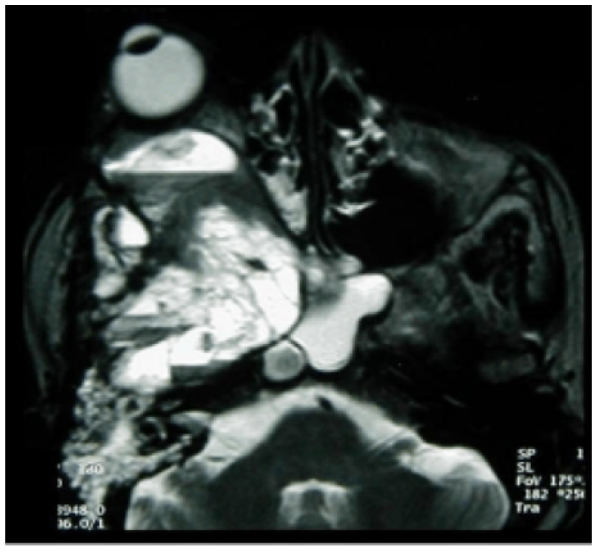


Figure 15a: Axial MRI showing a massive dumbbell shaped trigeminal neurinoma.

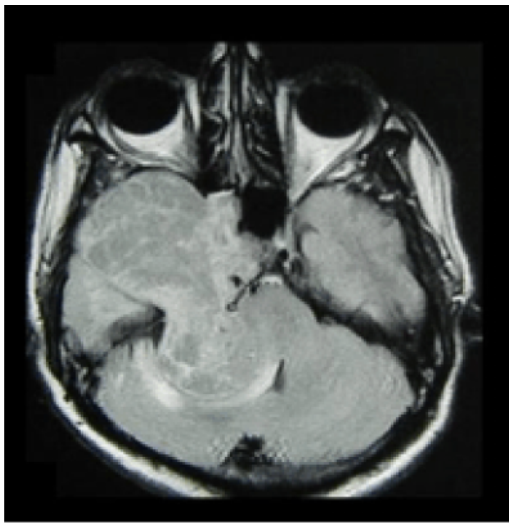


Figure 15b: T2-weighted axial MRI showing the tumor and its extensions. Postoperative scan showing te tumor resection.

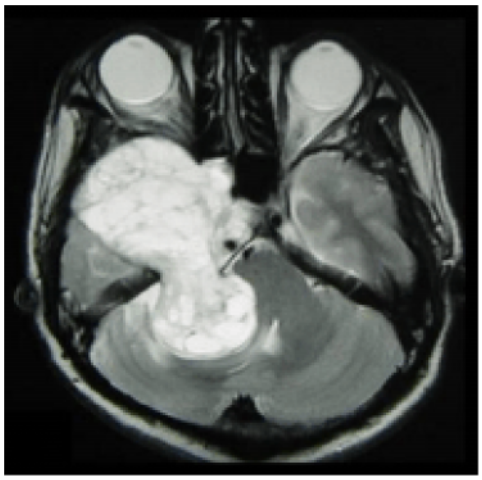
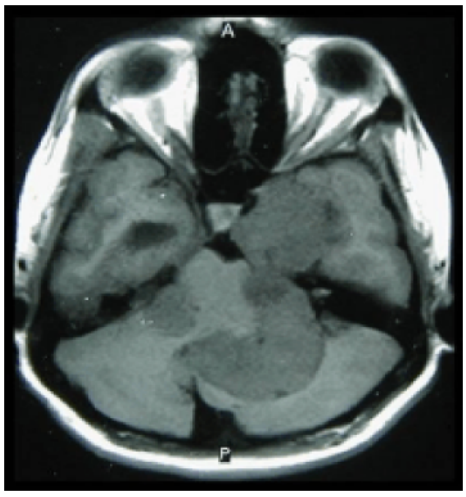


Figure 16a: MRI of a 19-year old girl with NF2. It shows multiple neurinomas that include fourth, fifth and bilateral seventh and eighth neurinomas.

Figure 16b: Contrast enhanced scan showing the lesions vividly.



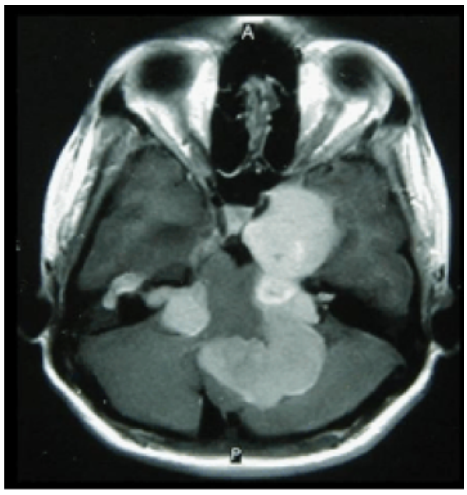
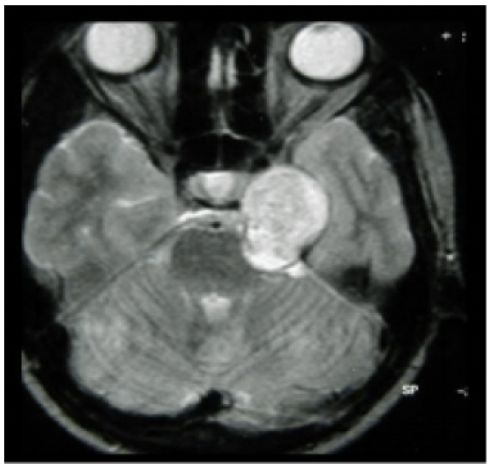


Figure 17: Axial MRI showing a relatively small trigeminal neurinoma.

Figure 18a: Coronal T2 weighted MR image showing an extracranial trigeminal neurinoma extending into the pterygopalatine fossa along the foramen rotundum.



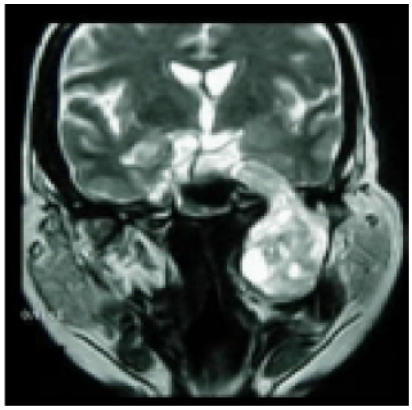


Figure 18b: Axial T2- weighted image showing the tumor and its extension along the maxillary division of the nerve.

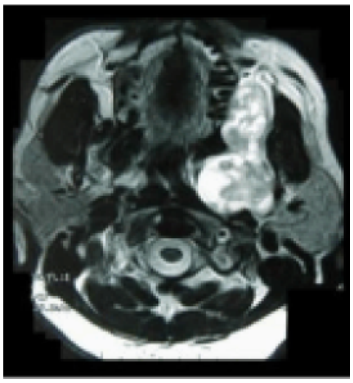


Figure 19b: Sagittal T2 –weighted MR image showing the tumor.

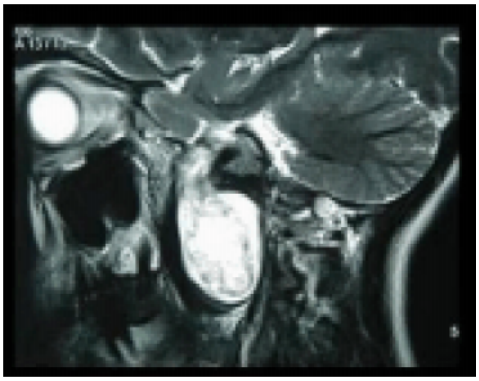
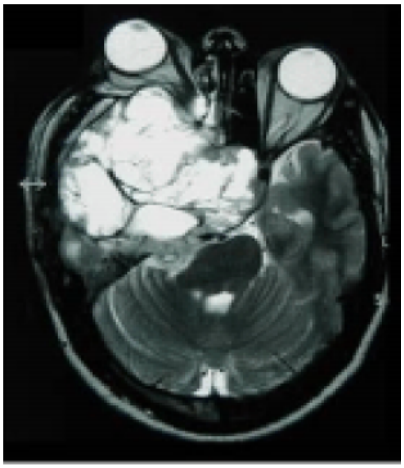


Figure 20b: Axial T2-weighted image showing the marked necrotic nature of the tumor.



cause new deficits, had improved rates of cranial nerve preservation, and often improved presenting symptoms. This therapy was not employed in our series, even in cases with demonstrated residue. On the basis of our experience, we believe that radical tumor

Figure 19a: Coronal T1-weighted MR image obtained in a 42 year old woman showing the trigeminal neurinoma extending into the infratemporal fossa along the mandibular division of the nerve.

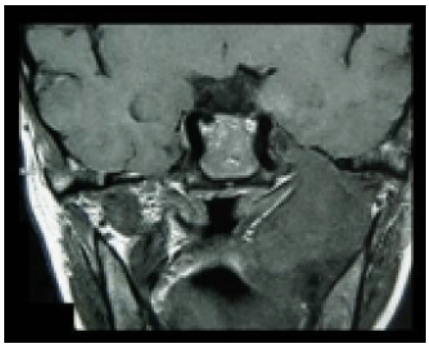
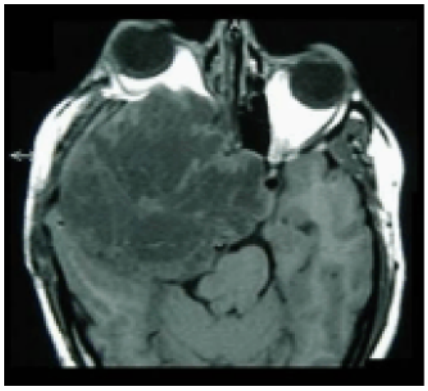


Figure 20a: Axial T1-weighted MR image obtained in a 30-year-old man showing a large trigeminal neurinoma extending up to the temporal convexity and into the orbit. Note the proptosis.



surgery for trigeminal neurinomas is safe and that excellent neurologic outcome and long-term tumor control can be expected.

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Markers of Endothelial Disorder after Subarachnoid Hemorrhage Sequential Changes and Impact of Open and Endovascular Surgery

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Abstract

Objective: The goal of this study was to investigate the markers of the endothelial cell disorder after subarachnoid hemorrhage (SAH) and the impact of open and endovascular surgery to the vasculature after SAH. Methods: 50 patients were enrolled in this prospective study. 25 patients underwent open surgery and Guglielmi detachable coil embolization, respectively. Serial blood samples were collected on post SAH days 0, 1, 7, and 14. von Willebrand factor (vWF), plasminogen activator inhibitor-1 (PAI-1), E-selectin levels were determined as markers of endothelial cell perturbation. The levels of 6-keto prostaglandin F1 alpha (6-ktPG) were measured as a marker of endothelial cell function. Results: The symptomatic vasospasm was observed in nine patients (six in open surgery and three in endovascular surgery). In both treatment strategies, the serum levels of vWF were elevated from day 0 to day 14. Serum levels of PAI-1 and E-selectin were higher in open surgery than endovascular surgery in day 7 and 14 significantly ($p<0.05$). The serum levels 6-ktPG were higher in endovascular surgery than open surgery in day 4 and 7 significantly ($p<0.05$). Conclusion: Elevation of parameters on endothelial perurbation and coagulopathy were recognized in both procedures. The inhibition of fibrinolysis by PAI-1, the expression of adhesion molecule, and endothelial dysfunction were higher in open surgery than endovascular surgery. This preliminary result suggests that endothelial disorder associated with open surgical procedure may be predominant than endovascular surgery. running title: Endothelial disorder after SAH.

Keywords: endothelial disorder, subarachnoid hemorrhage, endovascular surgery, surgery, open surgery, vasospasm.

Endovascular surgery has emerged as an alternative therapeutic modality of ruptured cerebral aneurysm. It was reported that the outcome in terms of survival free of disability at one year is significantly better with endovascular coiling (19) and it can also reduce the incidence of vasospasm (20,45). The reasons for this knowledge are that brain damage and the manipulation of arteries required during open surgery may result in unfavorable vascular affect after subarachnoid hemorrhage (SAH) (26). However, it is not clear what happens between such therapeutic assault and the vascular response. Traumatic brain injury such as a mild concussion initiates a cascade of acute and chronic injury responses which include disturbances in the cerebrovasculature that may result in the activation of the endothelial development of a dysfunction endothelium (3). In the pathophysiology of cerebral vasospasm following SAH, endothelial disorder and inflammatory mechanisms which may contribute to cerebral ischemia in experimental SAH has been appreciated (1,11,25).

By producing chemoattractants, expressing adhesion molecules in endothelial cells and increasing the permeability of the endothelial monolayer, inflammatory cytokines activate and attract leukocytes to vessel walls that injure the endothelium and contribute to further thrombus formation and endothelial damage (17). Von Willebrand factor (vWF) is a large adhesive glycoprotein which is suitable circulating marker of endothelial cell perturbation because of its sensitivity, its long half-life, and its relative specificity for endothelial cells(5,30,31). The

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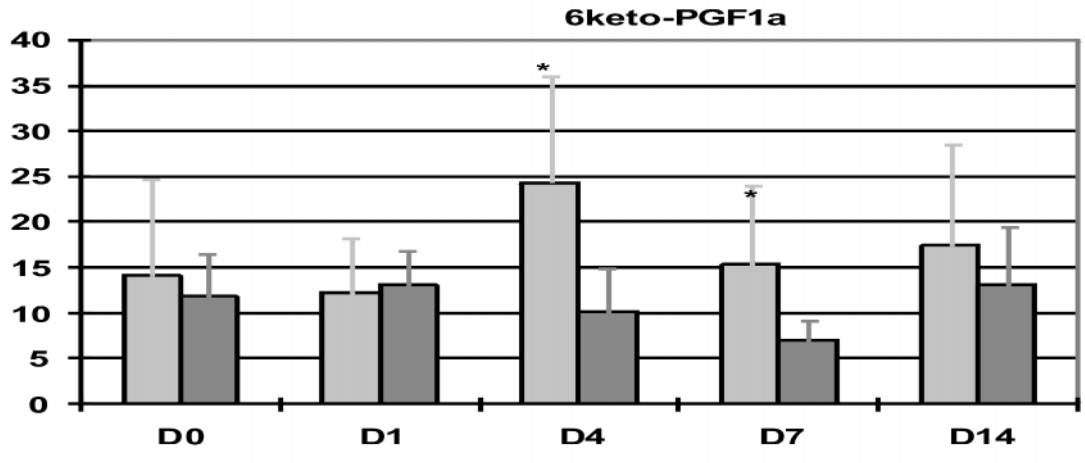
endothelial production of tissue plasminogen activator (t-PA) is increased during ischemia and thrombin stimulation (5). Plasminogen activator inhibitor-1 (PAI-1) is expressed in endothelial cells due to the action of thrombin and cytokines (16, 21). Fibrinolytic activity is regulated by the balance between t-PA and PAI-1 (8). The selectins are transmembrane glycoproteins expressed on activated vascular endothelium (P and E-selectin), activated platelets (P), activated leucocytes (L), and are involved in rolling and activation of leukocytes (22). The detections of E-selectin in serum and cerebrospinal fluid after SAH were reported (32). Vasoprotective function of endothelial cells is associated with biosynthesis and release of nitric oxide (NO), prostacyclin(PGI2), prostagrandin E2(PGE2), and carbon monoxide(CO). These endothelial mediators calm down activated platelets and leukocytes, prevent the occurrence of thrombotic events, promote thrombolysis, maitain tissue perfusion and protect vascular wall against acute damage and against chronic remodeling (10). The expressions of vWF, PAI-1, and selectin in endothelial cells are excellent circulating markers of endothelial cell perturbation and 6-keto prostaglandin F1 alpha (6-ktPG) which is the metabolic product of PGI2 are suitable to investigate the endothelial function.

To evaluate the differences of therapeutic assault to the vasculartur, we prospectively compared the markers of endothelial perturbation which generates an imbalance in coagulofibrinolysis, the expression of adhesion molecules, and the endothelial dysfunction between open surgery and endovascular surgery.

Patients and Methods

Patients

50 patients with SAH were enrolled in this study. All patients were treated within three days of SAH onset (25 underwent direct open surgery and Guglielmi detachable coil embolization, respectively). The patient selection was as the following: neurosurgeons judged that the patient was available in both treatment procedures based on the angio-architectural aspects. The treatment protocol after the operation was the same in both groups. The patients who had a rebleeding and/or had to be operated on again were excluded from the selection criteria. Clinical features from the 50 patients are summarized in Table.1. 8 men and 17 women, aged between 25 to 88 years (mean, 60.4 yr) were treated by endovascular surgery, and seven men and 18 women aged between 30 to 71 years (mean, 57.7 yr), underwent open surgery. None of them were administered with anti-spasmogenic drugs such as calcium channel blockers, papaverine, hydroxyfasdil or thromboxane A2 blockers. All patients were neurologically examined every day after admission. Delayed ischemic neurological deficit (DIND) was determined as a gradual development of focal neurological signs and / or deterioration in the level of consciousness. The occurrence of cerebral vasospasm was confirmed by conventional cerebral angiography in all patients. Nine patients developed DIND (six after direct open surgery and three after the endovascular procedure). The outcomes of them were one good recovery



(GR), one moderate disability (MD), and one severe disability (SD) in endovascular surgery, five GR and one SD in open surgery, respectively.

Data collection

Blood samples were collected on post SAH days 0, 1, 7 and 14 for the markers of endothelial perturbation, and days 0, 1, 4, 7, 14 for 6-ktPG after receiving informed consent from each patient. Plasma isolated by centrifugation at 500g for 10 minutes was stored at -30 degrees C. We assayed serum concentrations of endothelial marker and a marker of endothelial function using commercially available kits. Serum levels of vWF were measured using STALIA test vWF (DIAGNOSTICA STAGO, Asnier-sur-seine, France). The total PAI-1 levels were measured using Latex photometric immunoassay-tPAI kits (Yuka Medias Co., Tokyo, Japan). Serum levels of E-selectin were measured using Parameter Human soluble E-selectin Immunoassay kits (R and D Systems Inc., Minneapolis, USA). 6-ktPG were measured using 6-keto prostaglandin F1 alpha (^{125}I) radioimmunoassay kit (PerkinElmer ™life Science, Boston,USA).

Data are presented as means±standard deviation and were analyzed using the chi-square test and Student's t test. A p value less than 0.05 was considered significant.

Results

Levels of markers on endothelial disorder

In both open and endovascular procedure, levels of serum vWF elevated over normal range (50%-145%) from day 0 to 14th after the onset of SAH (Fig.1). The differences between open surgery and endovascular surgery were not significant, however, there was a tendency towards an increase in its expression in patients

Fig. 1: Sequential changes of von Willebrand factor (vWF) after open and endovascular surgery. Normal range of serum vWF is between 50% and 145%. The serum levels of vWF increased in both open and endovascular surgeries in all days. The significant differences between open surgery and endovascular surgery were not found.

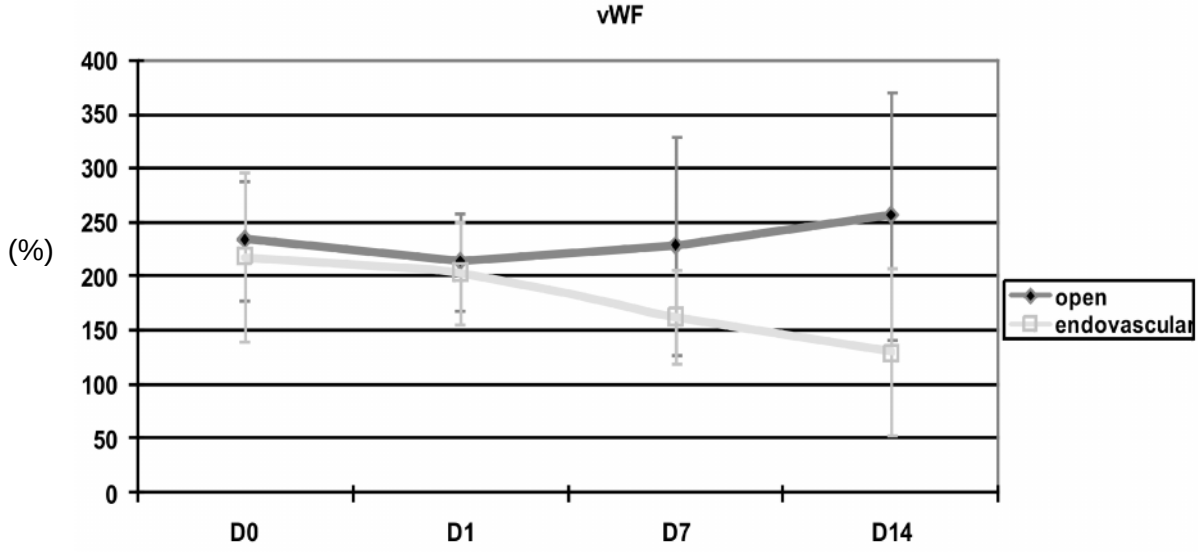


Fig. 2: Sequential changes of serum plasminogen inhibitor-1 (PAI-1) after open and endovascular surgery. Normal range of plasma PAI-1 is below 50ng/ml. Serum levels of PAI-1 after open surgery were over 50ng/ml between 0 to 14 days whereas those after endovascular surgery were within the normal range. Difference was significant day 7 (65.2±49.1ng/ml vs. 32.3±12.5ng/ml, p=0.0125)and day 14 (63.67±27.4ng/ml vs. 39.3±13.3ng/ml, p=0.002).

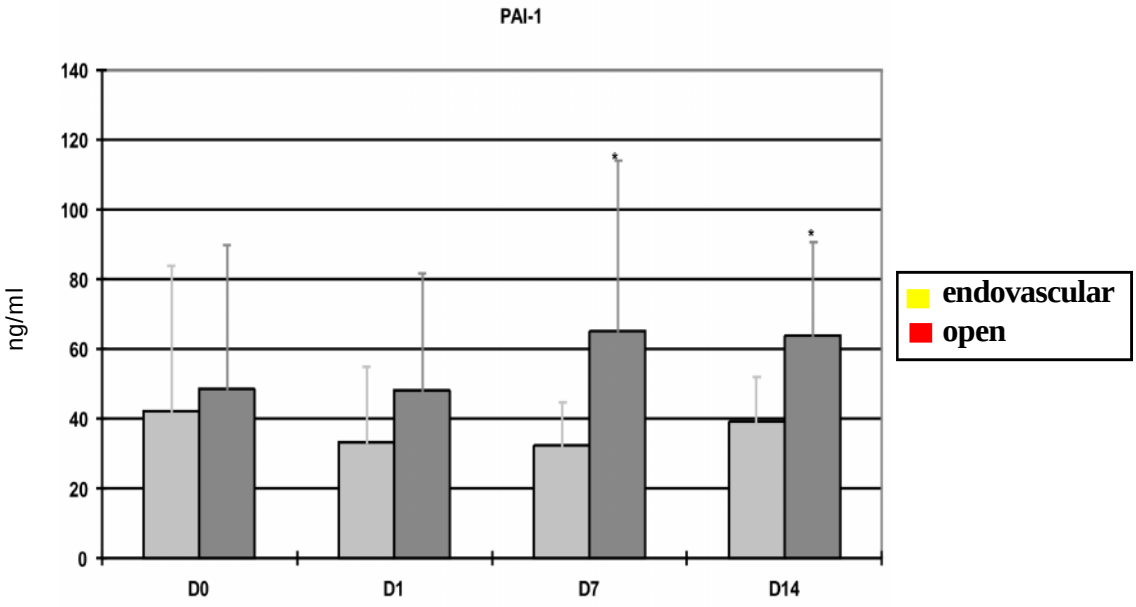


Fig. 3: Sequential change of E-selectin after open and endovascular surgery. Normal range of serum E-selectin is between 29.1ng/ml and 63.4ng/ml. Serum levels of E-selectin in open surgery were higher than endovascular surgery between 0 and 14 days following SAH, and the difference was significant on day 7 (63.6±37.6ng/ml vs. 40.8±24.7ng/ml, p=0.039).

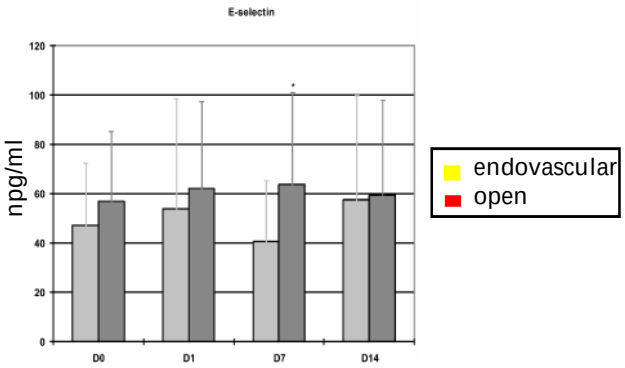
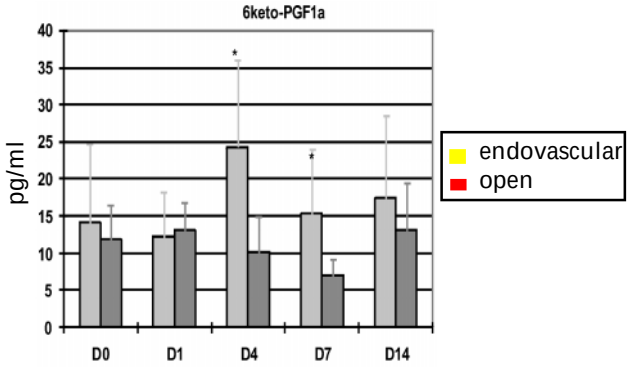


Fig. 4: Sequential changes of 6-keto prostaglandin F1 alpha (6-ktPG) after open and endovascular surgery. Serum levels of 6-ktPG in open surgery are lower than endovascular surgery between 1 and 14 days following SAH, and the difference was significant on day 4 (10.2±4.7pg/ml vs. 24.3±11.7 pg/ml, p=0.01) and day 7 (7.0±2.1 pg/ml vs. 15.4±8.7 pg/ml, p=0.03).



that underwent open surgery.

Levels of PAI-1 obtained after endovascular surgery were below 50ng/ml between days 0 and 14 after the onset of SAH. These data were within the normal range. However, the serum levels of PAI-1 obtained after direct open surgery were higher than endovascular surgery in all days. Differences between the two procedures were significant on day 7 (65.2±49.1ng/ml vs. 32.3±12.5ng/ml, p=0.0125) and day 14 (63.67±27.4ng/ml vs. 39.0±13.3ng/ml, p=0.002) (Fig.2).

The serum levels of E-selectin in open surgery were higher than endovascular surgery between 0 and 14 days following SAH, and the difference was significant on day 7 (63.6±37.6ng/ml vs. 40.8±24.7ng/ml, p=0.039) (Fig. 3).

Levels of a marker of endothelial function

Serum levels of 6-ktPG in open surgery are lower than endovascular surgery from day 4 to day 14, and significant differences are recognized on day 4(10.2±4.7pg/ml vs. 24.3±11.7pg/ml, p=0.01) and day 7 (7.0±2.1pg/ml vs. 15.4±8.7pg/ml, p=0.03) (Fig.4).

Relationship between markers of endothelial perturbation and DIND

Statistical analyses showed a significant difference between patients with DIND and without DIND in 6-ktPG on 7th day (p=0.03), but did not show a significant difference regarding the markers of endothelial perturbation.

Discussion

Enodothelial perturbation after SAH

The endothelium is an active paracrine organ that produces potent vasoactive, procoagulant, anticoagulant and proinflammatory substances. Endothelial cells have two important roles, namely adaptive and constitutive functions. During acute inflammation, endothelial cells assume adaptive functions. They become chemoattractants, facilitating leukocyte adhesion, activation and migration, and also become prothrombotic and demonstrate vascular permeability. Levels of coagulation factors, inflammatory cytokines and adhesion molecules during vasospasm following SAH are elevated (1, 4, 6, 13, 22, 37). These reports support the notion that the activation of endothelial cells following abnormal stimulation after SAH gives rise to this adaptive function. PAI-1 and vWF are expressed in endothelial cells through the action of thrombin and cytokines (34). The production of E-selectin in endothelial cells is increased by inflammatory cytokines and E-selectin is released into serum as a soluble type (17). Therefore, the elevation of these circulating markers indicates that the endothelial perturbation following activation is predominant. The relationship between the markers of endothelial perturbation and SAH has been recognized (4, 6, 11, 28, 29, 31, 37, 42). The endothelial cell perturbation in brain was found in mild concussive injury (3) and multiple sclerosis (7). Even though the mechanisms of cerebral endothelial perturbation are not clear, many direct and indirect results of injury such as impact on cerebral vessels, hemodynamic stress, hypoxia, cerebral ischemia, or brain edema are posited (46).

Endothelial dysfunction after SAH

The constitutive function of normal endothelial cells prevents vascular permeability, regulates vascular tone by producing PGI2 and NO, and suppresses inflammation, endovascular thrombosis by controlling the production of t-PA and PAI-1, and intimal proliferation for regulation of vascular metabolism. The present study shows the endothelial dysfunction after open surgery is more predominant than after endovascular surgery, because serum 6-ktPG levels were significantly reduced in open surgery. The level of 6-ktPG on 7 day in the patients with DIND was statistically lower than in the patients without DIND. After the acute inflammatory state,endothelial NOS and cyclooxygenase 1 down-regulation causes reduced PGI2 and NO production (43). Sasaki described a mechanism associated with endothelial damage in the major cerebral arteries with regard to the pathogenesis of vasospasm (35). Several reports indicate that the diminished synthesis of PGI2 and NO caused by endothelial dysfunction is associated with cerebral vasospasm after SAH (12, 24, 35, 38, 44, 45). Thromboxane synthetase inhibitor increases plasma levels of 6-ktPG (41). Fasudil is an anti-spasmogenic drug that prevents the development of endothelial injury (36). These reports support the notion that endothelial dysfunction associated with endothelial perturbation plays an important role in cerebral vasospasm following SAH.

Hematological component and SAH

The hematological component is a key factor in the pathophysiology of cerebral vasospasm. In normal brain tissue fibrinolytic activity is low (40), whereas thromboplastic activity is extremely high in comparison with other organs (2). Hirashima et.al reported that the hypercoagulation state is associated with cerebral vasospasm (13). Thrombosis formation in the artery of vasospasm was confirmed in autopsy cases and experimental study (27,29). Ikeda et.al reported the elevation of serum and

CSF levels of PAI-1 in the patients with SAH(14). vWF acts as a bridging adhesive molecule between platelets and components of the extracellular matrix or other platelets, and it may become the cause of pathological thrombus formation leading to arterial occlusion (33). Artery-to-artery embolism, such as high intensity transient and microembolic signals, have been confirmed using transcranial Doppler sonography during the period of DIND (9). Patients who underwent either open or endovascular surgery had serum vWF elevation. It showed the tendency towards procoagulopathy after the occurrence of SAH and it was promoted by the elevation of serum PAI-1 in open surgery.

Cereberal vasospasm and therapeutic assault

Cerebral vasospasm is an important causative factor of morbidity and mortality in patients with SAH. Blood in the subarachnoid space and the degradation product of hemoglobin spreading over the vessels may contribute to the development of symptomatic cerebral vasospasm. Removing blood from the subarachnoid space should be useful as a treatment of vasospasm (18, 23). On the other hand, physiological stress such as brain damage, manipulation of arteries and disturbance of peripheral cerebrospinal fluid circulation during open surgery may contribute to the occurrence of vasospasm after SAH (15, 26). In addition, it has been reported that the incidence of cerebral vasospasm following SAH can be reduced by endovascular surgery (20, 45). But, what happens between therapeutic assault and the vascular response remains unclear. When the endothelium is physically disrupted or functionally damaged, prothrombotic and proinflammary state is characterized by platelet and leukocyte activation and adhesion (expression and upregulation of vWF and E-selectin), promotion of thrombin formation, coagulation and fibrin deposition at the vascular wall (expression of PAI-1), and unprotected state of vascular wall (reduction of PGI2). Our study suggested these inflammatory disorders of endothelial cell following SAH were boosted by open surgery than endovascular surgery. However, whether endothelial disorder is a casual or indirectly related factor in the pathogenesis of cerebral ischemia after SAH is still uncertain. Actually, in the present study we could not recognize significant differences between patients with and without vasospasm in sequential changes of these endothelial perturbations after SAH. Further study is needed to clarify the relationship between the incidence of vasospasm and therapeutic assaults in larger series of patients.

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