

Diagnostic MR imaging features of craniocerebral *Aspergillus* of sino-nasal origin in immunocompetent patients

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Summary

Background. Craniocerebral invasive *Aspergillus* of sino-nasal origin has been reported with a very high mortality due to a peculiarly fulminant clinical course. Early diagnosis based on clinical radiological imaging may have an impact on final clinical outcome. This retrospective study focuses on characteristic MR imaging features of *Aspergillus* (of sinonasal origin) in immunocompetent patients.

Methods. Medical records of patients were reviewed retrospectively during the period from 1991 to 2003 in the two tertiary care hospitals. All the patients had radiological evidence of disease in the paranasal sinuses with or without intracranial extension. Immunocompetence of patients was assessed on clinical and radiological data. MRI scans (n = 20) were reviewed by both clinical neurosurgeons and neuroradiologists separately. MRI was done on 1.5 tesla scanners and both T2-weighted and T1 weighted sequences were obtained followed gadolinium enhanced images. Patients were categorized into three types based on their anatomical location on MRI scans; type-1 being intracerebral, type-2 as intracranial extradural and type-3 invading orbit and/or skull base only. All these patient had the epicenter of disease in the nose and/or paranasal sinuses as evident on MR imaging. All patients underwent standard surgical intervention followed by antifungal therapy. Clinical outcome was assessed on Glasgow outcome scale with mean duration of clinical follow up of 13.9 months.

Findings. Mean age of patents (n = 20) was 31.1 years with male preponderance (3:1). MRI scans showed evidence of disease in paranasal sinuses including mucosal thickening (n = 11) and complete filling of sinuses (n = 9). T2-weighted images showed extremely hypo-intense fungal mass (n = 19) while T1-weighted images had iso-intense signals (n = 18). Gadolinium-enhanced images showed bright homogenous contrast enhancement (n = 18) and peripheral ring enhancement pattern (n = 2). All patients underwent appropriated surgical procedures depending upon anatomical location followed by standard antifungal therapy. Tissue diagnoses were established by histopathology (n = 20) and culture growth (n = 5). Overall mortality remained 15 percent.

Interpretation. Craniocerebral *Aspergillus* of sinonasal origin has typical MR imaging features. These features include a mass lesion producing hypo-to-iso-intense signals on T1-weighted, extremely low

signals (hypo-intense) on T2-weighted images, with bright homogenous enhancement on post-gadolinium T1-weighted imaging. These features in the clinical background may be helpful in early diagnosis and management of *Aspergillus* of sino-nasal origin in immunocompetent hosts. Prospective clinical study is required to make firm clinical therapeutic recommendations.

Keywords: Sinonasa; craniocerebral; aspergillosis; magnetic resonance imaging; diagnostic features.

Introduction

Craniocerebral *Aspergillus* of sinonasal origin is a rare clinical entity in the apparently immunocompetent individuals [2, 11]. Most of the published clinical experience about invasive *Aspergillus* is derived from patients who had significant immunological deficiency and data on this relatively uncommon condition in immunocompetent hosts is clearly deficient [2, 3, 15, 21].

Craniocerebral *Aspergillus* with an epicenter in the nose or/and paranasal sinuses has a very high mortality of 13–50% [2, 11, 23]. Early diagnosis and hence an appropriate therapeutic strategy in this very particular condition has a crucial role on prognosis [2, 3, 9, 11]. Clinical spectrum in *Aspergillus* of sinonasal origin varies from a benign, non-invasive stage to a rapidly progressive and destructive fulminant variety [2, 4, 9, 13, 17, 23]. Invasive *Aspergillus* can involve the orbital cavity; destroy the skull base with or without extension into the cranial cavity [11, 13, 14, 17, 22, 23]. Initial evaluation by radiological imaging including computer-

Table 1. *Clinical features of Aspergillosis in different anatomical locations on MRI scans*

No	Location-type	Cases (n)	Predominant clinical features
1	Type-1 Aspergillosis	6	headache, facial pain, diplopia, cranial nerve deficits, papilloedema, focal neurological deficits, convulsions
2	Type-2 Aspergillosis	5	headache, nasal stuffiness, anosmia, nasal discharge, ophthalmoplegia, loss of vision impaired conscious level
3	Type-3 Aspergillosis	9	nasal stuffiness, nasal discharge, proptosis, periorbital pain, diplopia, anosmia, proptosis, visual loss, malar swelling

ized tomography (CT) scan and magnetic resonance imaging (MRI) are done in the initial battery of the investigations [1, 12, 25]. Therefore, it is conceivable that identification of peculiar radiological diagnostic features in this condition will provide a concrete clinical base to embark on specific management, leading to a definite impact on the final clinical outcome.

Only a few case reports and short case series have described radiological features of *Aspergillosis* of paranasal sinuses to differentiate it from other similar pathologies of paranasal sinuses [2, 7–11, 17, 19, 21]. To our knowledge, this is the largest series, which describes radiological features in histopathologically proven cases of craniocerebral *Aspergillosis* of sinonasal origin in immunocompetent patients. The aim of this retrospective review is to identify the peculiar diagnostic features of craniocerebral *Aspergillosis* of sino-nasal origin in immunocompetent patients on MRI.

Material and methods

Twenty cases of craniocerebral *Aspergillosis* of sino-nasal origin in immunocompetent host were treated during the period from January 1990 to June 2003 (12.5 years) at the Aga Khan University, Karachi, Pakistan. The Aga Khan University Hospital is one of the major tertiary care hospitals with a catchment population of more than 10 million.

Clinical and radiological records of 134 cases were reviewed who had been diagnosed as having invasive *Aspergillosis*. The study included all those patients who: 1) were at least 15 years of age of both sexes 2) had radiological evidence of disease essentially in the nose and/or paranasal sinuses invading the orbit or the skull base with or without extension into the cranial cavity (extradural location) and/or into the brain parenchyma (intradural location) 3) had immunocompetence indicated by absence of any concomitant or previous chronic disease e.g. diabetes mellitus, renal failure, cirrhosis, malignancy, as well as the absence of any history of intravenous drug abuse, use of immunosuppressive or steroid therapy, organ transplantation, and HIV infection 4) no clinical and radiological evidence of systemic fungal infection e.g. no pulmonary *Aspergillosis* on routine X-ray chest. Other screening tests (e.g. CT scan of chest) were only done if there was clinical suspicion of systemic/disseminated *Aspergillosis* 5) had been proved to have invasive *Aspergillosis* either on histopathology or on culture as opposed to having “allergic” sinus *Aspergillosis*. The latter were excluded.

MR images of all the 20 cases of established *Aspergillosis* were reviewed retrospectively by a team of clinical neurosurgeons and neuroradiologists. These patients were categorized into three groups based

on anatomical location and extent of disease on radiological imaging as follows;

1. *Type-1 Aspergillosis*: Sino-nasal disease with *intracerebral Aspergillosis* without being contiguous.
2. *Type-2 Aspergillosis*: Sino-nasal disease contiguous with *intracranial extradural* extension.
3. *Type-3 Aspergillosis*: Sino-nasal disease with *orbital and/or skull base* bony invasion/destruction only.

Magnetic resonance (MR) scans were done on a 1.5-Tesla scanner (Toshiba *Visart-V3.51**, *R253*). All these images were obtained as

Table 2. *Diagnostic features of Aspergillosis of sino-nasal origin on MRI scans*

MRI features	Number of cases
1. <i>Signals on T-1 sequence</i>	
– Iso-intense	18
– Iso-to-hypo-intense	2
2. <i>Signals on T-2 sequence</i>	
– Extremely Hypo-intense	19
– Iso-to-hypo-intense	1
3. <i>Contrast enhancement pattern</i>	
– Bright homogenous	18
– Ring pattern with central hypo-intense signals	2

Table 3. *Summary of results of management and clinical outcome*

Patients' parameter	No. of cases
<i>Surgical procedures</i>	
FESS (Fiberoptic endoscopic sinus surgery)	8
Craniotomy	4
External ethmoidectomy	4
Trans-sphenoidal	2
Lateral orbitotomy	1
Burr-hole biopsy	1
<i>Antifungal therapy</i>	
Type-1 <i>Aspergillosis</i> (amphotericin B plus oral itraconazole)	9
Type-2 <i>Aspergillosis</i> (oral itraconazole alone)	5
Type-3 <i>Aspergillosis</i> (oral itraconazole alone)	6
<i>Clinical outcome</i> (Glasgow Outcome Scale)	
Good recovery	10
Moderate disability	7
Death	3
<i>Duration of follow up</i>	13.9 (0.25–41) months

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multisection, T1-weighted and T2-weighted images. The T1-weighted images were obtained with repetition times (TRs) of 300–500 msec and echo time (TEs) of 5–15 msec. The T2-weighted images had TRs of 2500–5000 msec and TEs of 80–120 msec. The maximum acquisition matrix was 256 to 256. The section thickness was 5 mm with an intersection gap of 1–2 mm. Axial, coronal and sagittal

images were obtained in all the cases in which MRI was done. Contrast enhancement with gadopentate dimeglumine (Omniscan™, Nycomed imaging AS Oslo-Norway) was used in every MR imaging study.

Diagnosis of *Aspergillosis* was established by histopathological analysis and immuno-staining of biopsied tissues (with Periodic Acid-Schiff

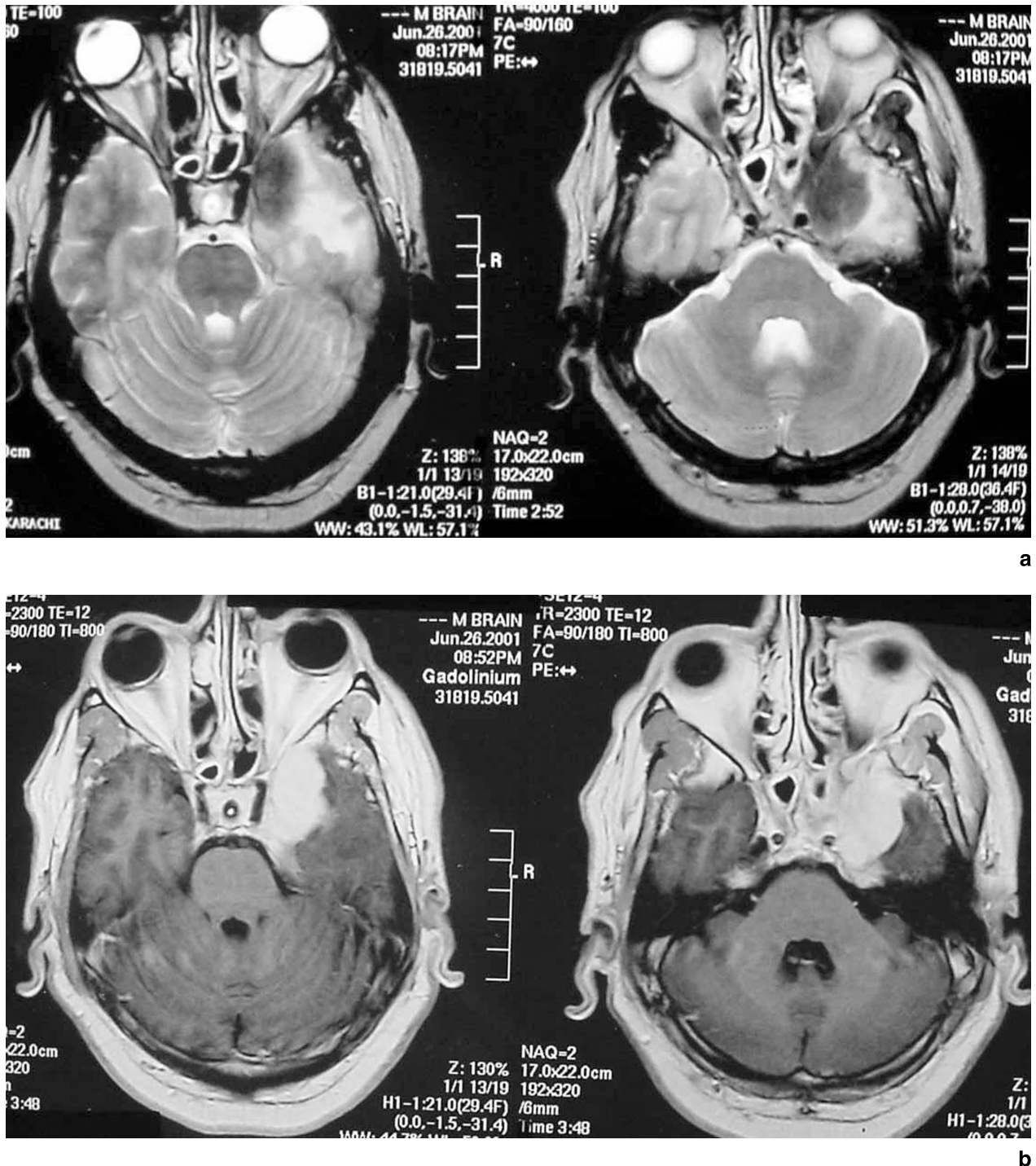
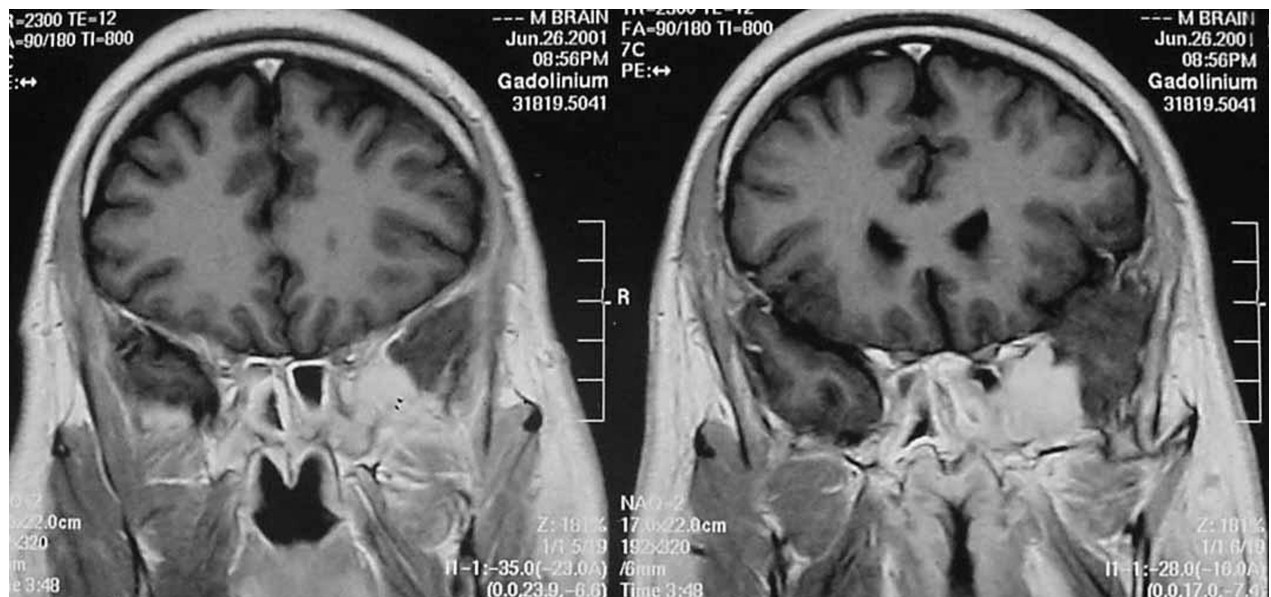


Fig. 1. (a) T-2 weighted MR imaging (axial sections) showing a mass lesion in the left middle cranial fossa producing extremely hypo-intense signals. (b and c) Post-gadolinium enhanced T-1 weighted image (axial and coronal sections) of the same patient (as in a) showing bright contrast homogenous enhancement of the mass lesion. There is also involvement of the adjacent sphenoid sinus with mucosal thickening



c

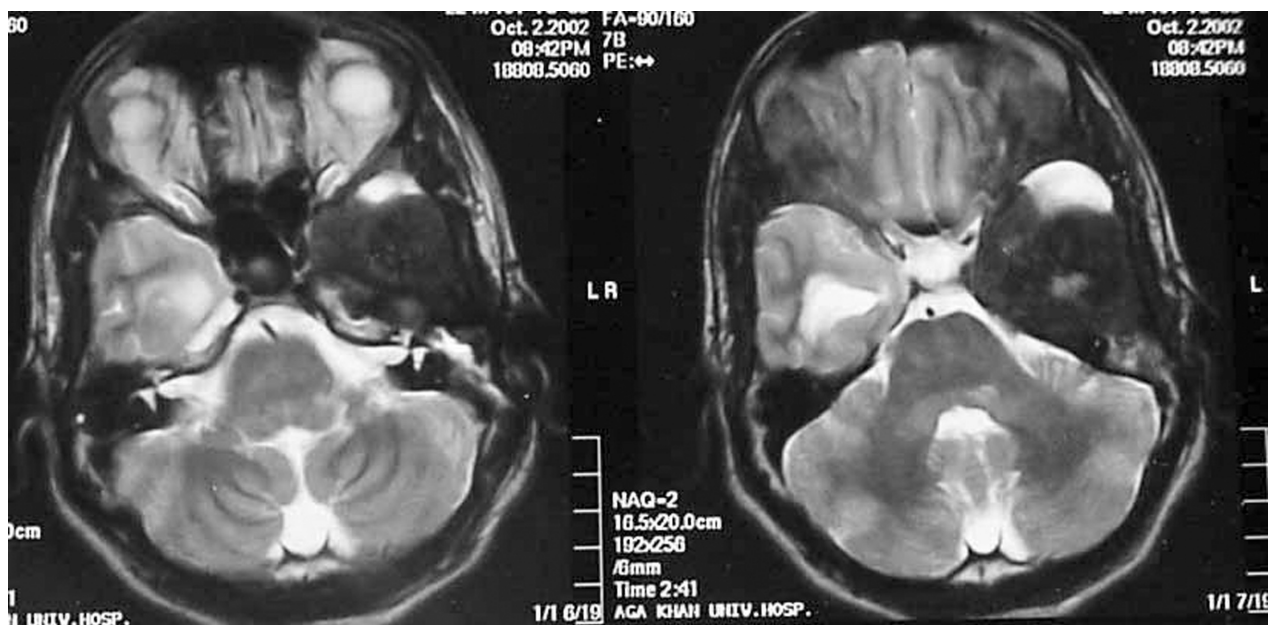
Fig. 1 (continued)

and Grocott-Gomori methenamine-silver nitrate stains). Septate fungal hyphae branching at right angles were considered consistent with the diagnosis of *Aspergillosis*. Twenty patients had histopathology and 5 patients showed *Aspergillus* growth on cultures.

All the cases were managed by a multidisciplinary approach involving the “fungal team” which included a neurosurgeon, an ENT surgeon and an infectious disease physician.

Surgical intervention was carried out by appropriate surgical procedures, depending on anatomical location and extent of disease.

In all patients with type-1 *Aspergillosis* (intracerebral), the initial antifungal therapy consisted of intravenous amphotericin B deoxycholate (Fungizone, Bristole-Myers Squibb, Princeton, New Jersey) with a total dose of 3 grams. The daily dose administered ranged between 0.5–2.5 mg/kg/day (with initial single test dose of 0.1 mg/kg) and



a

Fig. 2. (a) T-2 weighted MR image (axial section) of a patient showing a mass lesion in the left paracavernous region and giving extremely hypointense signals. There is also mucosal thickening of adjacent sphenoid sinus. (b and c) Post-gadolinium enhanced image (axial and coronal sections) of the same patient (as in a) showing bright homogenous contrast enhancement of the left paracavernous mass lesion. Adjacent sphenoid sinus is also showing filling of mass giving similar contrast enhancement

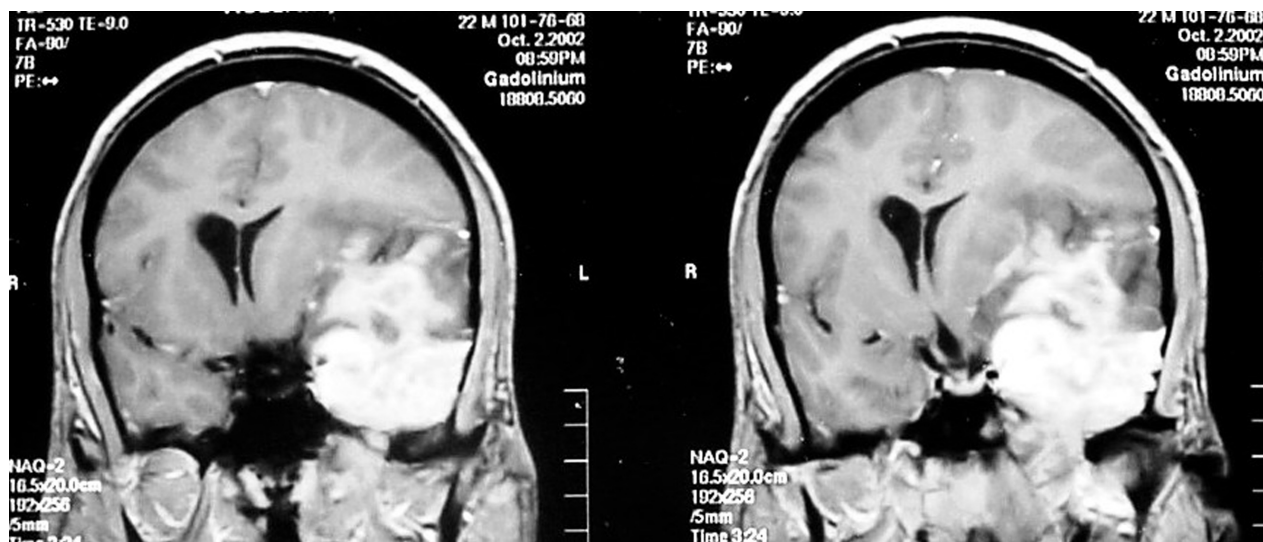
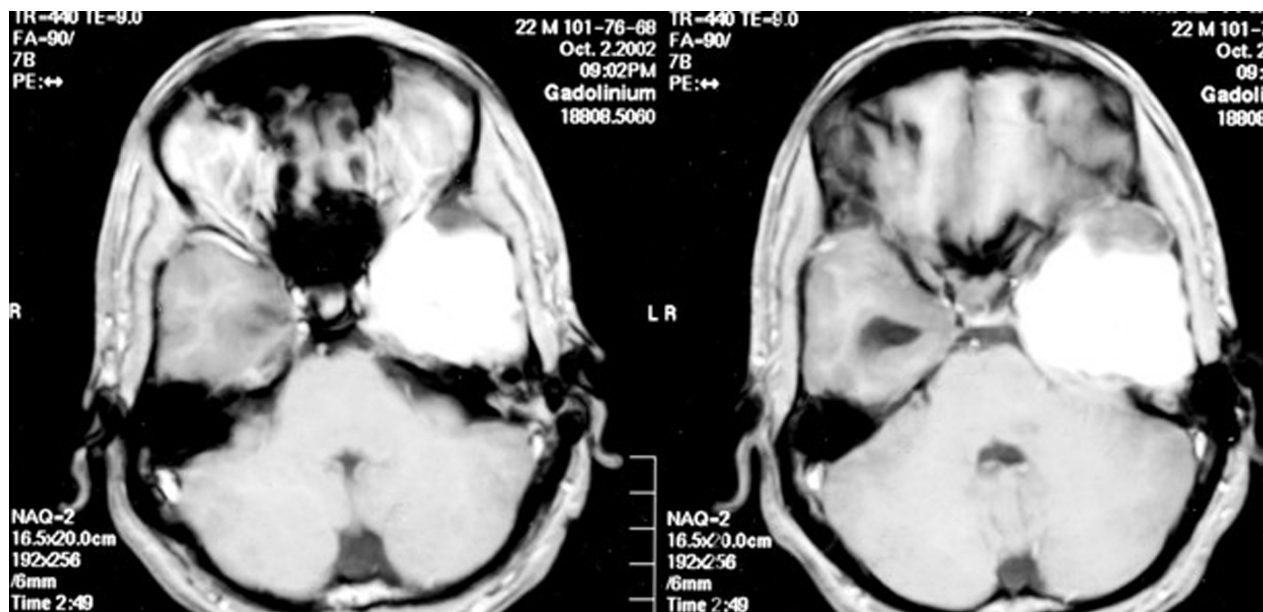


Fig. 2 (continued)

was titrated according to clinical tolerance and renal function of patients. This therapy was followed by oral itraconazole 400–800 mg/day (Sporanox Capsules, Janssen Pharmaceutical, Beerse, Belgium) in divided dosage for 8–12 months. All patients with type-2 and type-3 *Aspergillosis* were treated with oral itraconazole alone.

Clinical outcome was assessed by Glasgow Outcome Scale (GOS). The patients were followed in clinics with mean duration of follow up of 13.9 (0.25–41) months.

Results

Mean age of patients in 20 cases was 31.1 (15–74) years with male preponderance (3:1). Clinical manifes-

tations depended on the location of the disease and are summarized in Table 1.

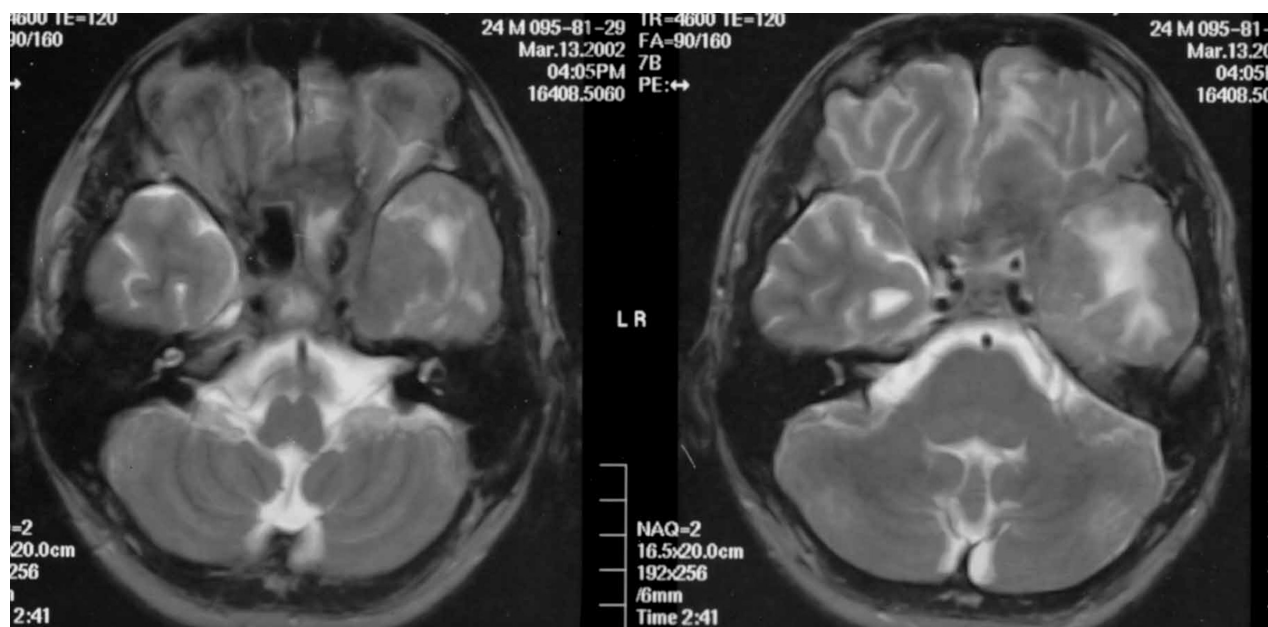
Routine X-ray chest (postero-anterior view) was done in all patients to screen for pulmonary lesions of *Aspergillosis*. CT scans of chest were done in only eight cases either due to clinical suspicion of pulmonary *Aspergillosis* or suspected *Aspergillus* infiltrates on screening chest X-rays. In all cases, these were negative.

In computerized tomographic scans, bony erosion of sinus walls and/or skull base was seen in 17 patients while calcifications within the fungal mass were present

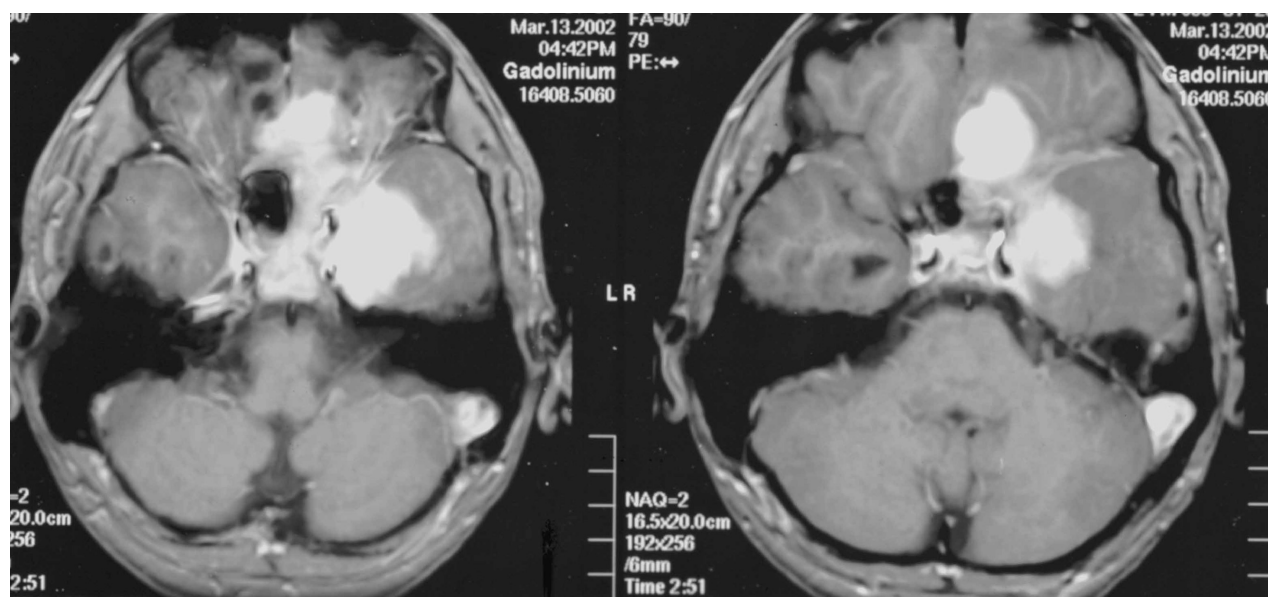
in three patients. Contrast enhancement in CT scans was seen in 18 patients.

MRI scans of brain were done in 20 patients. There was definite evidence of disease in all the cases in the para-nasal sinus ranging from mucosal thickening (n = 11) to complete filling of sinuses with the *Aspergillus* mass (n = 9). The fungal mass lesions were extreme-

ly hypo-intense on T2-weighted images (n = 19) and iso-to-hypo-intense in one patient. On T1-weighted images, the lesions were iso-intense in 18 patients and iso-to-hypo-intense in two patients. On T1-weighted post-gadolinium imaging, the lesions showed homogenous bright enhancement in 18 patients and 2 patients showed peripheral ring enhancement in post contrast



a



b

Fig. 3. (a) T-2 weighted MR imaging (Axial sections) showed a iso-to-hypo-intense mass lesion in the left paracavernous region and also extending subfrontally into the anterior cranial fossa. (b and c) Post-gadolinium enhanced T1 weighted MR images (axial and coronal sections) showing bright homogenous enhancement of the same mass lesion. The contrast enhanced mass is also filling the sphenoid sinus

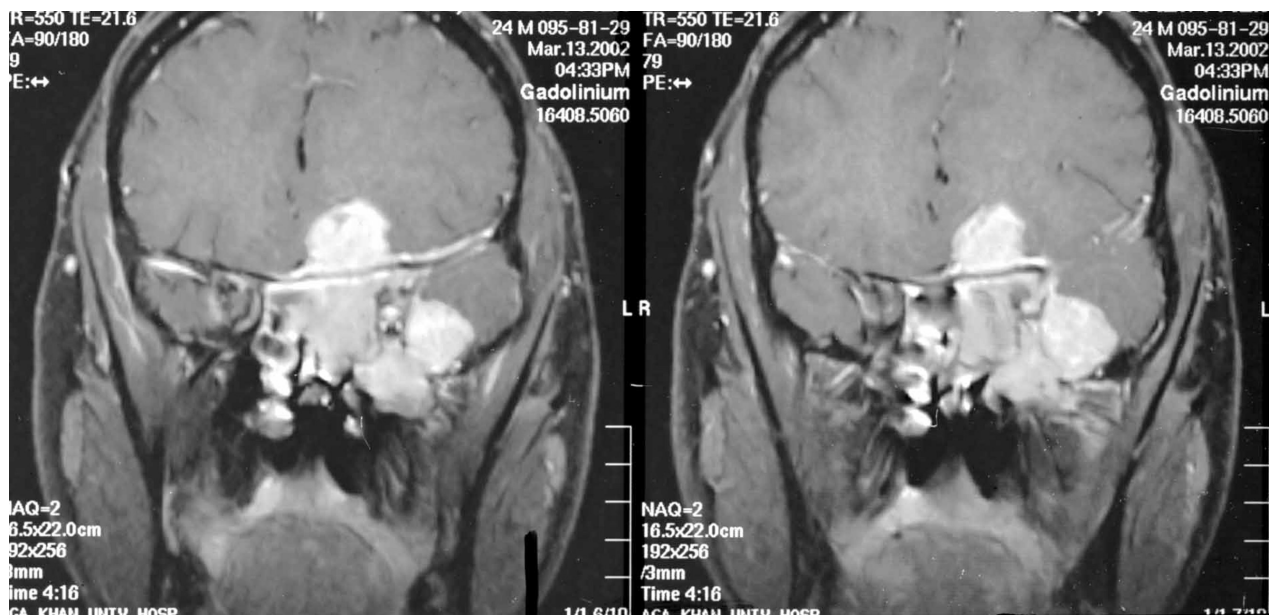


Fig. 3 (continued)

images. MRI features of *Aspergillosis* were summarized in Table 2. All the lesions in type-2 *Aspergillosis* were extra-axial (extradural) in location and it was confirmed preoperatively.

Histopathological studies and immuno-staining of fungal material revealed fungal hyphae branching at acute (45 degrees) angles. Other prominent features

included the presence of non-caseating granulomatous inflammation along with epithelioid and multinucleate giant cells. These features were seen in all the biopsy specimens (of 20 patients). Histopathological diagnoses were established in all 20 patients while culture growth was also positive for *Aspergillus flavus* in 5 patients.

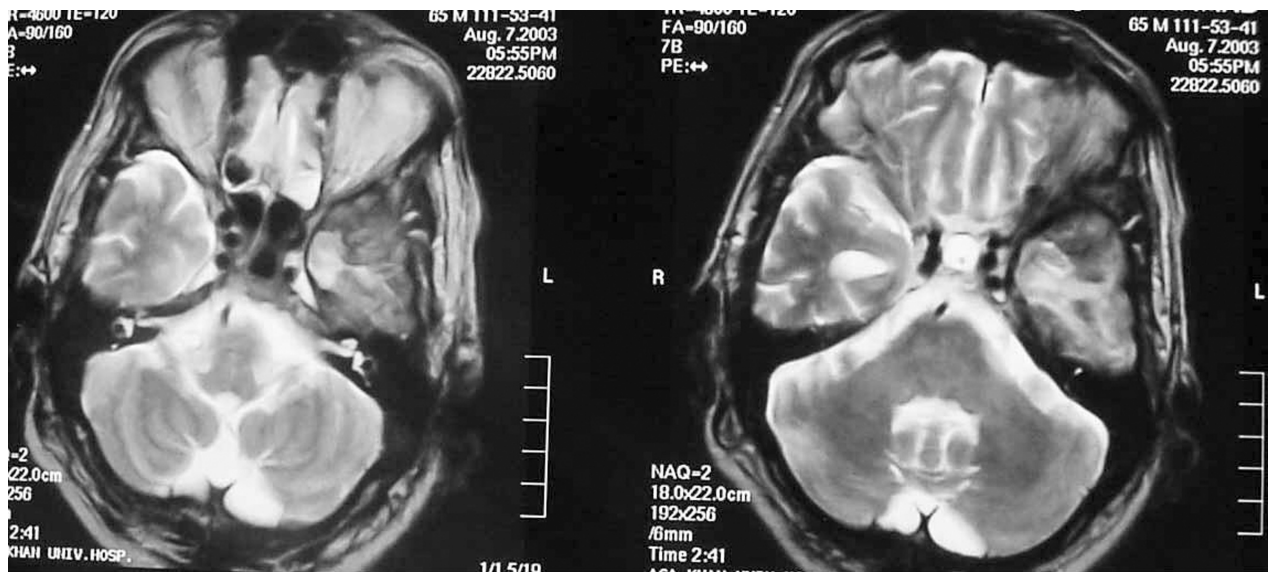


Fig. 4. (a) T-2 weighted MR imaging (axial section) showing a hypo-intense mass lesion located in the temporal region, lying medially with extension on the lateral aspect of cerebral cortex saddled on the sphenoid ridge. (b and c) T-1 weighted Post-contrast imaging (axial and coronal sections) showed a significantly bright enhancement of the same mass lesion. There is also meningeal enhancement adjacent to the mass. Sphenoid sinus mucosa is thickened and showing enhancement

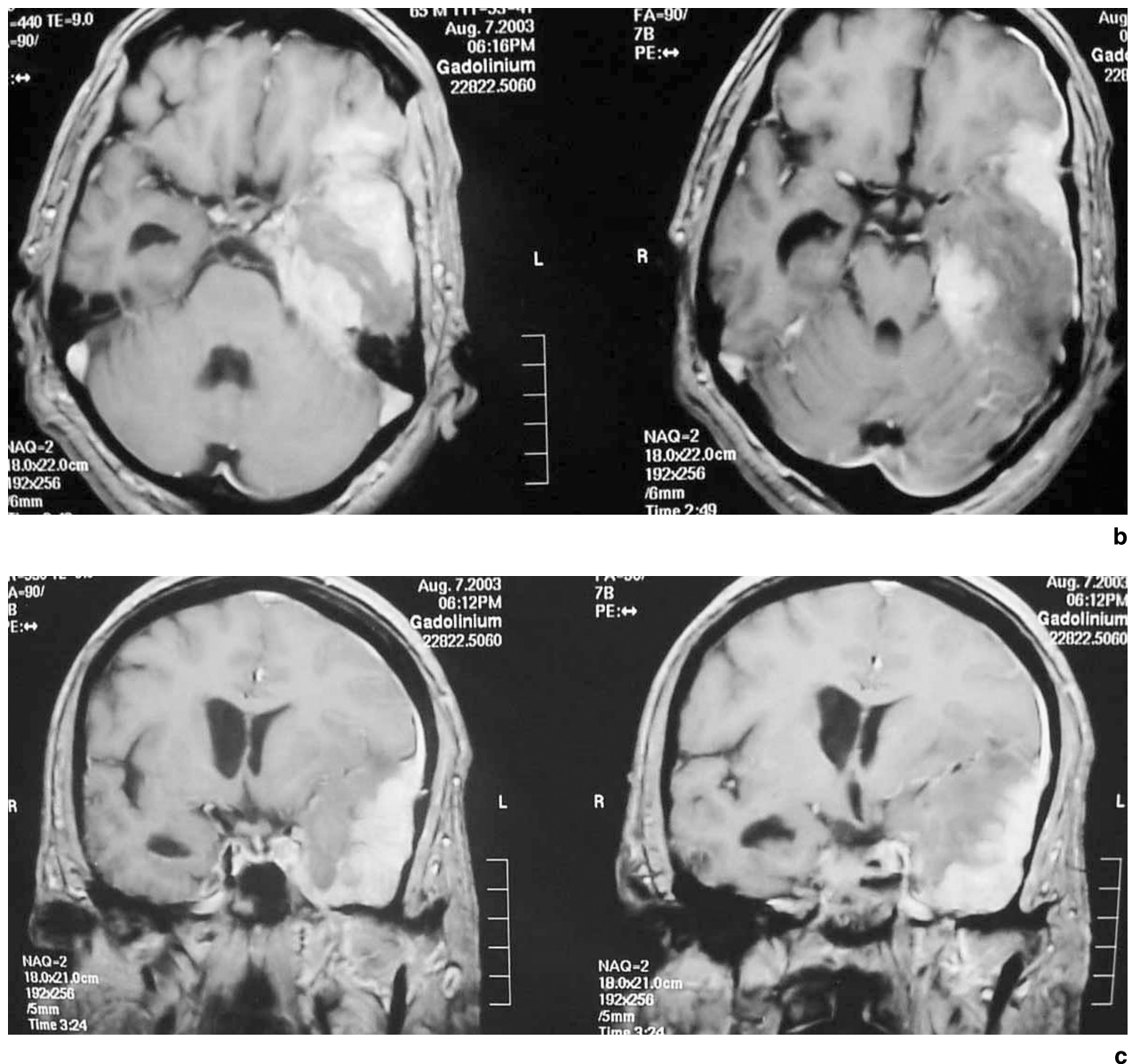


Fig. 4 (continued)

Surgical intervention was carried out in all the 20 patients and the choice of surgical procedures was made according to anatomical location. Surgical procedures aimed at the partial debulking of *Aspergillus* mass. Three patients with Type-1 (intracerebral) *Aspergillus* died during the course of Amphotericin B treatment within 1–3 weeks. The cause of death was intracranial complications *Aspergillus* including multiple cerebral infarctions, intracerebral hemorrhage and widespread multifocal dissemination in the brain parenchyma and ventricles. Overall mortality remained 15% with mean duration of clinical follow up of 13.1 months. Results are summarized in Table 3.

Discussion

Hora and Houston [10] first recognized the primary *Aspergillosis* of paranasal sinuses, which can be non-invasive or invasive type. The invasive type may present with extension into the cheek, orbit, or cranial cavity and is manifest radiologically as a paranasal mass contiguous with their adjacent extension into orbital or cranial cavity [10, 11, 13–15]. The invasiveness is usually described in immunologically compromised cases [1, 25] but there has been a recent surge of these cases in the apparently immunocompetent individual as well [2, 11, 23].

There is uncertainty as to why *Aspergillosis* becomes invasive in non-immunocompromised individuals [2, 11, 17, 23]. The impetus for a saprophytic colony of paranasal sinus *Aspergillosis* to become pathogenic is due to mechanical obstruction of the nose and paranasal sinuses

[17]. This can occur secondarily due to septal deviation, nasal polyps, infections, and allergic rhino-sinusitis [7]. Location has been cited as the cause for the more aggressive nature of sphenoid *Aspergillosis* because of the close relation to the skull base [7, 13]. However,

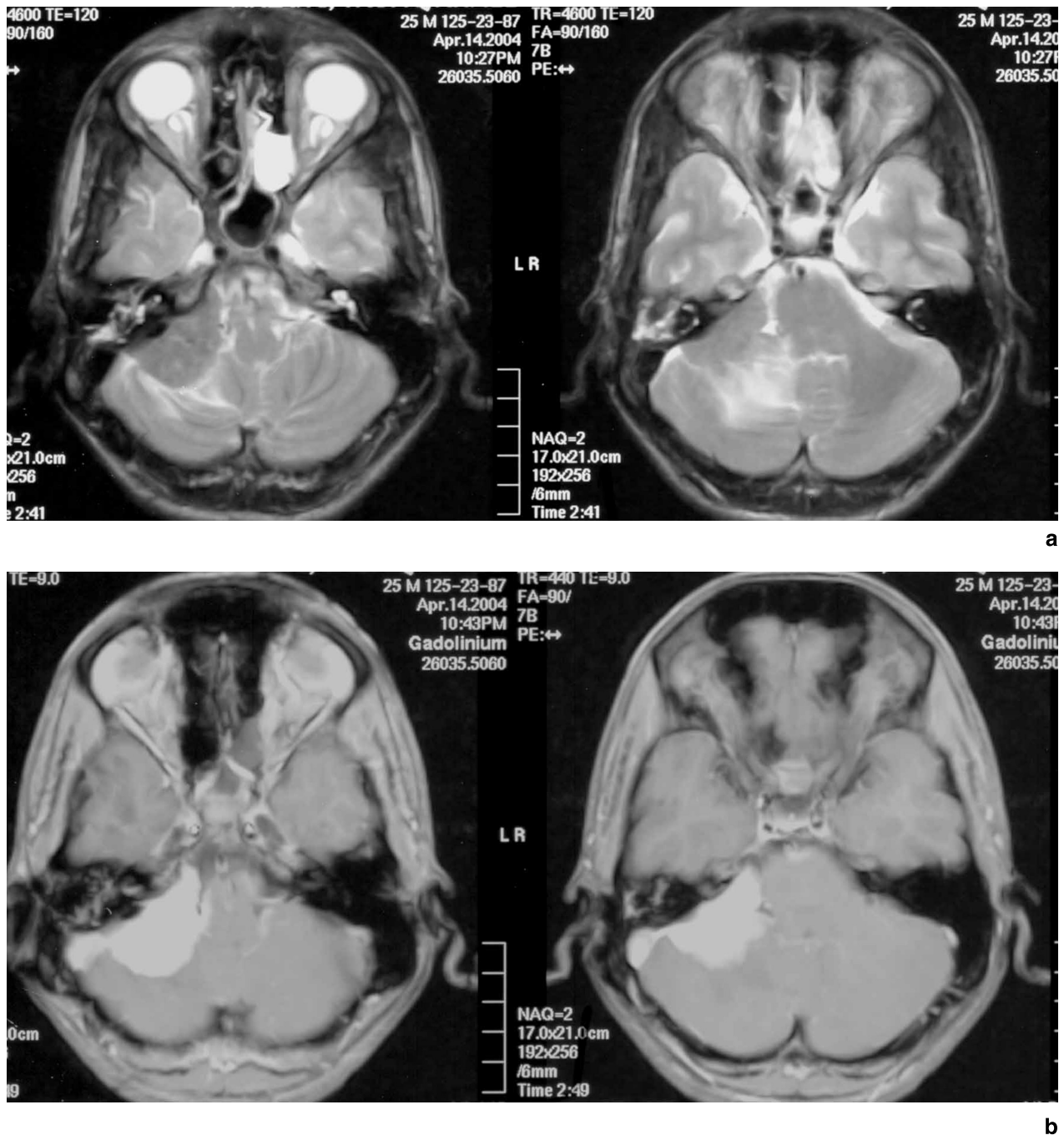


Fig. 5. (a) T-2 weighted MR imaging (axial sections) showing a mass lesion in the right cerebellopontine angle with broad base on the petrous bone. It is producing hypo-to-iso-intense signals with no peri-focal edema. (b and c) Post-contrast imaging (axial and coronal sections) with T-1 weighted sequence producing bright homogenous enhancement of the same mass lesion. There is associated dural enhancement and slight displacement of brain stem

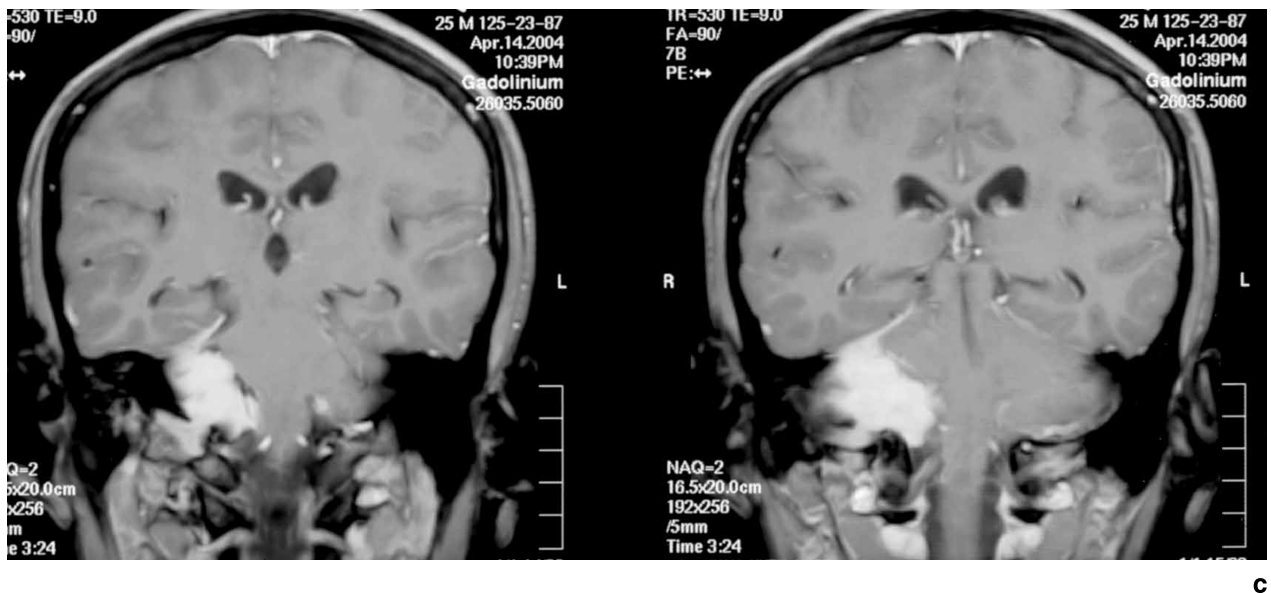


Fig. 5 (continued)

erosion of bone is not always necessary for the development of intra-cranial extension as the *Aspergillus* has the propensity to spread along vessels serving as direct channels for seeding of aspergilli [7, 17]. Stammberger *et al.* [20] described that the hyper-dense appearance of *Aspergillus* mass is due to local enrichment of metal ions and calcium salt (calcium phosphate and calcium soleplate) in necrotic areas of fungal masses.

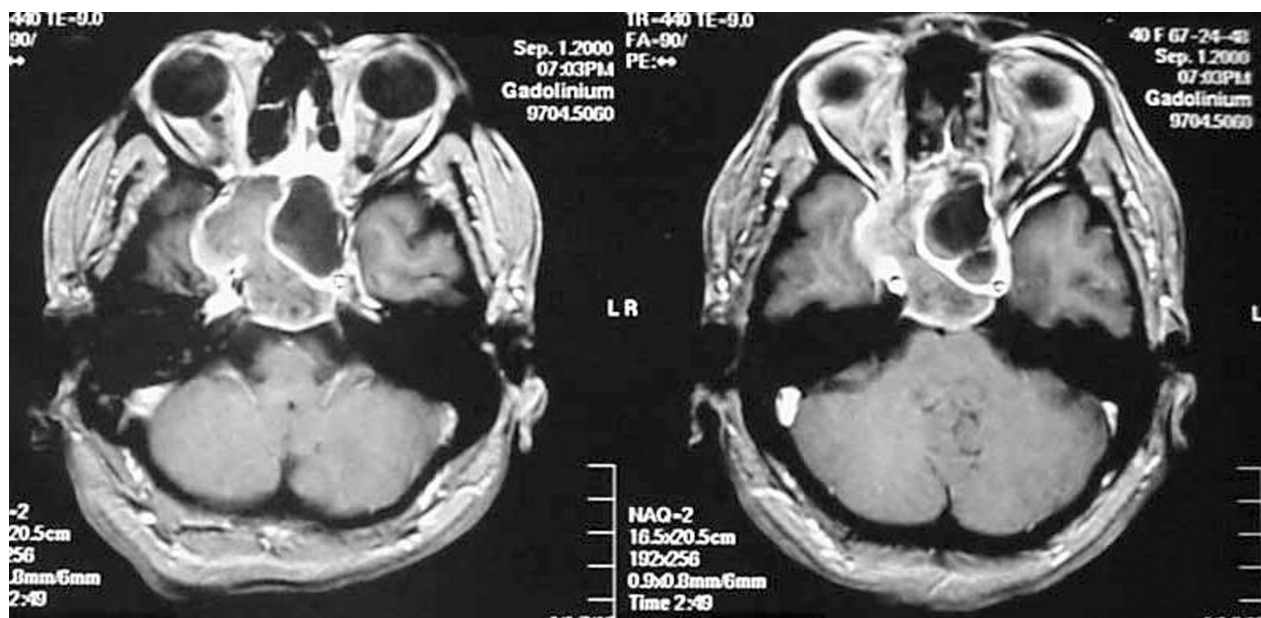
Although the CT scan appearance of *Aspergillus* mass may be non-specific. MR imaging features of *Aspergillo*sis of nasal and/or sino-nasal origin are very characteristic. In our series, the *Aspergillus* mass had iso-to-hypo-intense signals on T1-weighted images in 18 cases whereas it was extremely hypo-intense on T2-weighted images in all the cases except one. Even in this case the mass was relatively hypo-intense to muscle and neural tissue. Similarly, there was very bright homogenous contrast enhancement of the mass both in the sinus and its extension into the adjacent cranial and orbital cavities. MRI also showed that there was a definite epicenter of disease present in the para-nasal sinuses. These MRI features give the typical appearance of *Aspergillo*sis of sino-nasal origin and these proved to be diagnostic for the clinical background and manifestations of the disease.

The hallmark of diagnosis of *Aspergillus* mass on MR imaging are extremely hypo-intense signals on T2-weighted images. Zinreich *et al.* demonstrated that

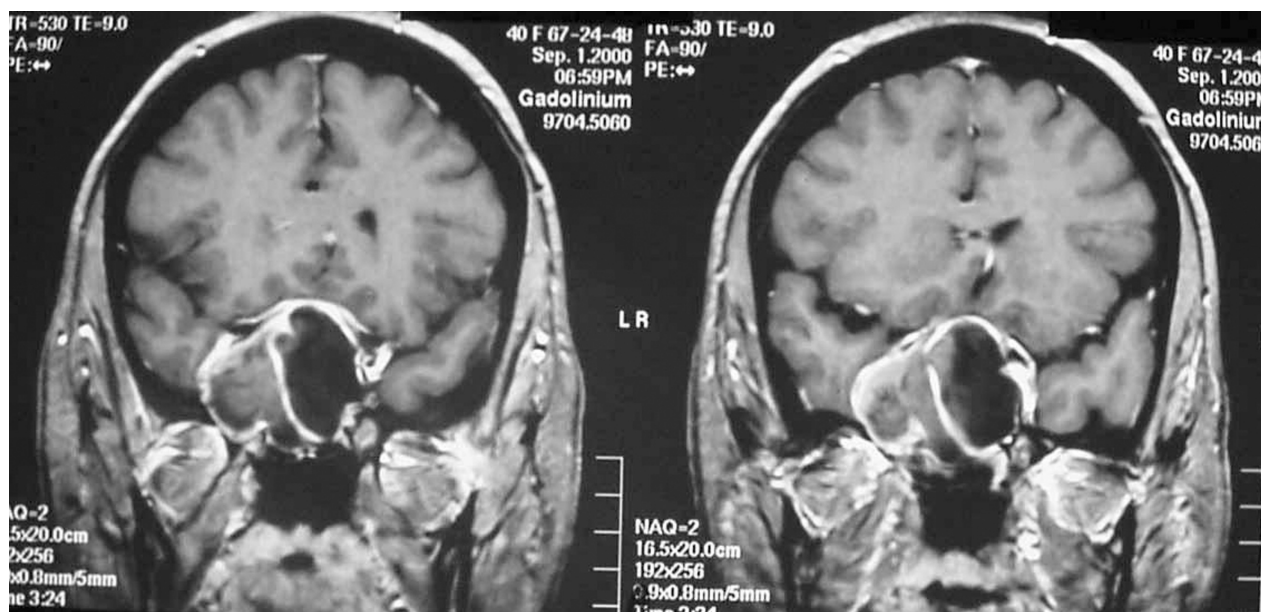
the decreased signal intensity on a T2-weighted image in *Aspergillus* mass was due to the presence of ferromagnetic elements such as iron, zinc, magnesium and manganese in high concentration [6, 26]. These elements are known to be essential in fungal amino-acid metabolism [5, 24]. The source and the mechanism of uptake of these metals by *Aspergillus* are still not clear [24, 26]. Som *et al.* further added that part of the explanation of the low signal was due to the dehydration effect that occurs in chronic inflammatory disease [5, 19, 20]. T1 and T2 relaxation times in these fungal masses are of the order of a few milliseconds, with T2 being shorter than T1 [19, 20].

Gadolinium enhancement is bright and homogenous in all our cases except in two cases, which showed ring enhancement like a true fungal abscess. The homogenous contrast enhancement is due to the solid nature of *Aspergillus* mass except in those with ring enhancement, which had the cystic nature of pus. These findings are confirmed peroperatively as well as on histology. The enhancement pattern had also been attributed to host-defense mechanisms, being more intense and bright in immunocompetent patterns [25]. This could also explain the bright homogenous contrast enhancement in all our cases with no apparent immunosuppression.

In our past clinical experience with craniocerebral *Aspergillo*sis of sino-nasal origin [18], we have managed a few cases conservatively without histopathological diagnosis and the diagnosis in these cases was solely



a



b

Fig. 6. (a) Post-gadolinium enhanced MR image (axial section) showing a ring-enhancing mass lesion lying in the sellar region with prefrontal and lateral extension. (b) Post-gadolinium enhanced MR image (coronal section) of the same patient (as in a) showing the same ring-enhancing pattern of mass with suprasellar extension

based on peculiar MR imaging features and clinical background. The patient received oral itraconazole, monitored by the clinical course and serial radiological imaging, which showed progressive decrease in size of the lesion. The overall mortality in our study remained 15%. The patients with Type-3 and Type-2 *Aspergillus* showed very good clinical recovery but three patients with Type-1 *Aspergillus* (intracerebral) died (Table 3).

So this anatomical classification of craniocerebral *Aspergillus* of sino-nasal origin seems to correlate with the final clinical outcome as described in our recently published data [18]. Clinical outcome on Glasgow outcome scale remains worst for type-1 *Aspergillus* (Intracerebral), intermediate for type-2 *Aspergillus* (Intracranial extradural) and good recovery is shown in type-3 *Aspergillus* (Orbital and skull base invasion) [18].

Conclusions

Craniocerebral *Aspergillus* of sino-nasal origin has typical MR imaging features. These features include a mass lesion producing hypo-to-iso-intense signals on T1-weighted, extremely low signals (hypo-intense) on T2-weighted images, with bright homogenous enhancement on post-gadolinium T1-weighted imaging and presence of disease process in nose and/or paranasal sinuses. This array of neuroradiological features with the clinical background may be helpful for early diagnosis and management of *Aspergillus* of sino-nasal origin in immunocompetent hosts. Prospective clinical study is required to make firm clinical therapeutic recommendations.

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