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MRI in COVID-19 associated acute invasive fungal sinusitis (AIFS): Diagnostic confidence, diagnostic accuracy and inter-observer agreement

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Abstract
Aim: To determine the diagnostic accuracy of MRI, degree of confidence in diagnosis and interobserver agreement in patients with COVID-19 associated acute invasive fungal sinusitis (AIFS).
Methods: Study was undertaken in a tertiary care hospital using retrospective case-control design. Cases were 68 confirmed AIFS patients and controls were 23 non-AIFS patients with concurrent or recent COVID-19 infection who underwent MRI scan of paranasal sinuses during a period of 8 weeks. MRI scans were independently reviewed by two consultant radiologists who were blinded to the clinical presentation, laboratory test results and nasal endoscopy findings. Detailed imaging parameters and predefined degree of confidence in diagnosis were recorded and analysed using SPSS software version 23.
Results: Sensitivity of the two radiologists (TP and SG) for MRI diagnosis of definite AIFS was 93% and 91% respectively and specificity was 100% for both. Sensitivity when using 'loss of contrast enhancement' to diagnose as probable or definite AIFS were 89% and 92% and when using 'extrasinosal involvement' were 91% and 90%, for TP and SG respectively. Specificity of both the MRI parameters was 100% for both radiologists. There was almost perfect statistical agreement between the radiologists for all imaging parameters (k = 0.84 to 0.97) and for degree of confidence in diagnosis of definite AIFS Vs possible AIFS Vs non-fungal (k = 0.88).
Conclusion: MRI is a highly sensitive and specific modality to diagnose AIFS with excellent interobserver agreement. Loss of contrast enhancement and extrasinosal involvement are two highly reliable MRI parameters in ascertaining diagnosis in the appropriate clinical scenario.

Keywords: Fungal sinusitis, invasive sinusitis, mucormycosis, MRI, sinus necrosis, COVID-19 associated mucormycosis

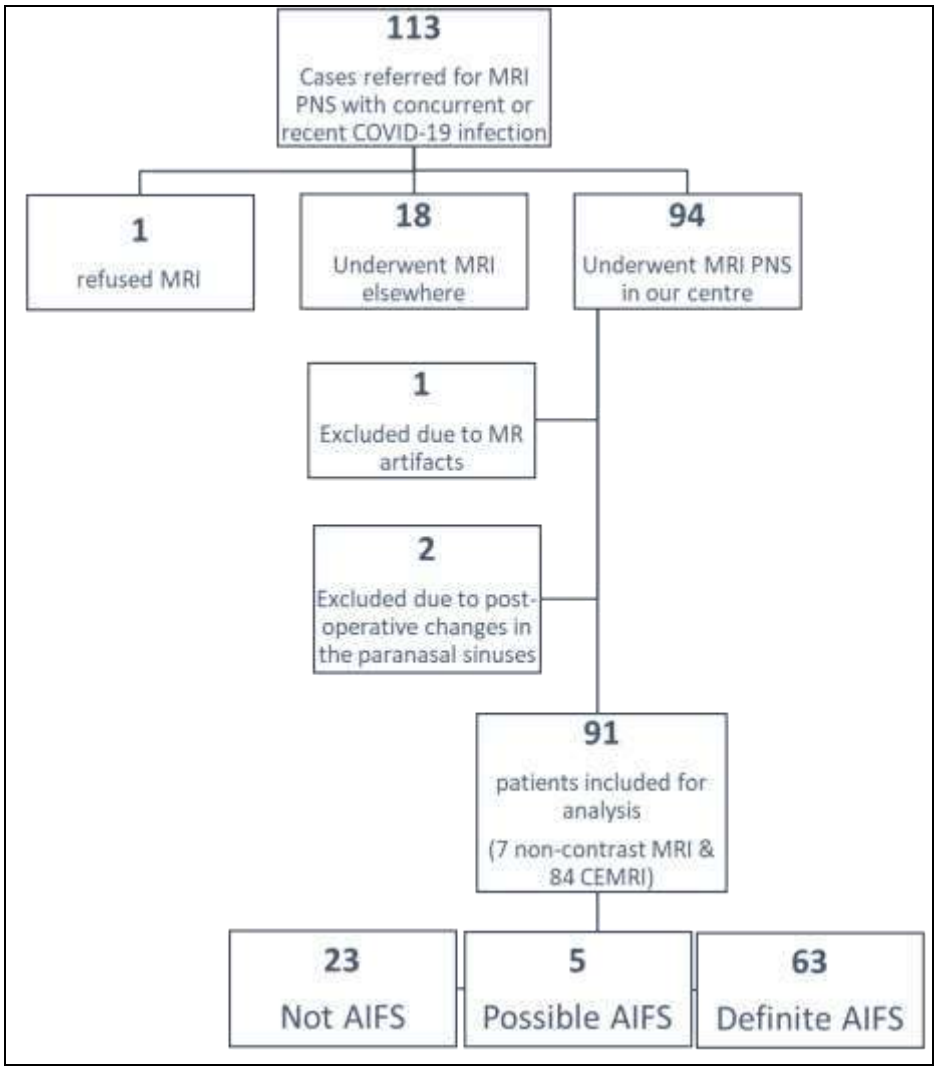
1. Introduction
Coronavirus disease 2019 (COVID-19) has left its mark globally with far reaching consequences on global health and economy. While the first series of COVID-19 associated acute invasive fungal sinusitis (AIFS) cases from India [1] was reported in February 2021, there has been exponential increase in AIFS cases (including rhino-orbital-cerebral mucormycosis, ROCM) making it an epidemic amidst the global pandemic. Baseline prevalence of invasive fungal sinusitis is 80 times higher in India than that of developed countries [2] and over 80% of the COVID-19 associated AIFS cases were contributed by India [3] which reveal the magnitude of this epidemic. It being a rare but deadly disease, most general radiologists would have seen only a handful of AIFS cases in the pre-COVID era. Owing to the nature of the disease, finding appropriate control group was not easy prior to this epidemic. Once COVID-19 associated AIFS has been described, there were increasing number of patients being referred to radiology departments to confirm or excluded AIFS, giving scope for a potential control group with clinical suspicion of rhinosinusitis and with history of concurrent or recent COVID-19 infection. Large volume of published literature concentrated on clinical aspects of this disease without dwelling much into imaging details. Through this case-control study, we aim to assess the diagnostic accuracy of each of the key MRI findings and determine the inter-observer agreement between radiologists when it comes to key MRI findings and in ascertaining the degree of diagnostic confidence as definite AIFS Vs possible AIFS Vs not AIFS.

2. Materials and Methods

Study was undertaken in a tertiary care hospital using retrospective case-control design. All patients had concurrent or recent COVID-19 infection (in the prior 2 months) and underwent MRI of paranasal sinuses (MRI PNS) in our centre during an 8 week period between 6th April and 2nd June 2021. 'Cases' were confirmed AIFS patients and 'Controls' were patients without any evidence of AIFS on imaging, nasal endoscopy or laboratory tests. Patients were excluded from the study if there was no MRI done in our centre (or) MRI was incomplete or uninterpretable due to artifacts (or) if patients had extensive post-operative changes in the paranasal sinuses from prior surgery. Four patients who had surgical defects limited to the nasal septum and/or nasal turbinates were included in the study. A total of 91 patients were included in the final analysis of which 7 underwent only non-contrast MRI and 84 underwent additional contrast enhanced MRI (CEMRI). Following flowchart shows the details of patient recruitment into the study.

The diagnosis in all 'cases' must be confirmed with either laboratory proof (direct microscopy, fungal culture, histopathological special staining or molecular diagnostics) or using a composite reference standard (including supportive clinical evidence, diagnostic nasal endoscopy, degree of confidence of diagnosis on MRI, intra-operative appearance and follow-up) when laboratory proof is not available. All MRI scans were performed on 1.5Tesla MRI magnet. Routine imaging sequences were obtained with dedicated sinus views: axial and coronal T1-weighted images with fat saturation, axial and coronal T2-weighted images with and without fat saturation, post contrast axial and coronal T1-weighted images with fat saturation.

MRI scans of all patients were independently reviewed by 2 consultant radiologists (TP and SG with 10 and 11 year experience respectively in independently reporting MRI scans) who were blinded to the clinical presentation, nasal endoscopy findings, intra-operative findings, laboratory test results and final diagnosis. Baseline demographic data and the following MRI parameters were recorded for each patient: a) Loss of contrast enhancement (LoCE) involving nasal turbinates, nasal septum or paranasal sinus walls suggesting necrosis b) Extrasinosal soft tissue with or without pterygopalatine fossa involvement c) Orbital involvement labelled as orbital cellulitis with or without orbital apex involvement and with or without optic nerve / optic nerve sheath involvement d) Cavernous sinus involvement e) Intracranial involvement and f) major vascular involvement (ICA thrombosis or vasculitis).



Degree of confidence in making a diagnosis of acute invasive fungal sinusitis on MRI was categorized as 1 = Not AIFS, 2 = Possible AIFS, 3 = Definite AIFS which were pre-defined as follows:

1. Not AIFS = Either normal sinuses or Non-fungal sinusitis

= Must fulfill all 3 criteria: No definite T2 hypointense fungal elements in the sinus wall or turbinates + No LoCE + No extrasinosal involvement.

2. Possible AIFS = Definite T2 hypointense fungal elements within the sinus wall or turbinates + No definite LoCE/unsure of LoCE + No definite/unsure of extrasinosal involvement.

3. Definite AIFS = Atleast 1 of the following two features unequivocally seen on MRI: LoCE (or) Extrasinosal involvement. In a non-contrast MRI, definite extrasinosal involvement must be present to categorise as Definite AIFS. T2 hypointense fungal elements in the wall may or may not be seen.

Detailed imaging parameters and predefined degree of confidence in diagnosis were recorded and analysed using Statistical package for the social sciences version 23 (SPSS Inc., USA). Statistical comparisons of demographic data between the case and control groups were made using X^2 (dichotomous variables) and unpaired *t* tests (continuous variables), with significance level of 0.05. Agreement between the 2 radiologists was compared using the Cohen's kappa coefficient (k). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy in classifying a patient as definite AIFS were calculated for each of the radiologists and for the two key MRI parameters.

3. Results

A total of 91 patients were included for analysis of which 23 were defined as 'controls' and 68 were defined as 'cases' based on final diagnosis. There was no significant difference in baseline demographic characteristics between the two groups (Table 1). None of the controls had microbiological or histological evidence of fungal sinusitis. Out of the 68 cases, 53 had laboratory proof of fungal organism (41 Mucorales, 9 Aspergillus, 2 with combined Mucor & Aspergillus infection, 1 Alternaria) while in 15 patients, final diagnosis was based on composite reference standard.

MRI findings of LoCE, extrasinosal involvement, orbital involvement, cavernous sinus involvement, intracranial involvement, major vascular involvement were seen in 60%, 62%, 49%, 32%, 28% and 9% respectively (consensus between the two radiologists). Representative MR images are shown in Figures 1-4. There was almost perfect statistical agreement between the two radiologists for all imaging parameters (k coefficient ranging from 0.84 to 0.97) and for degree of confidence in diagnosis of definite AIFS Vs Possible AIFS Vs Not AIFS (k = 0.88) (Table 2).

Sensitivity, specificity, PPV, NPV and overall accuracy for MRI diagnosis of definite AIFS was 93%, 100%, 100%, 82%, 94% and 91%, 100%, 100%, 79% and 93% for the two radiologists (TP & SG) respectively (Table 3). Sensitivity, specificity, PPV, NPV and overall accuracy when using LoCE to diagnose as probable or definite AIFS were 89%, 100%, 100%, 72%, 92% and 92%, 100%, 100%, 80%, 94% for TP and SG respectively and when using extrasinosal involvement to diagnose as probable or definite AIFS were 91%, 100%, 100%, 78%, 93% and 90%, 100%, 100%, 77% and 92% for TP and SG respectively (Table 3).

4. Discussion

Early literature on diagnostic imaging in the context of mucormycosis highlighted bone destruction as a key diagnostic feature on CT [4, 5]. However, as early as in 1986, it was clear that bone destruction on CT was a late finding and deep extrasinosal extension of disease beyond the bony sinus walls was common despite lack of bone destruction on CT [6]. Subsequently it was established that extrasinosal soft tissue involvement (commonly preantral and retroantral fat) on imaging is seen relatively earlier in AIFS patients, it possibly is the best individual predictor of invasive fungal sinusitis on CT [7], and may even be the sole radiologic finding [8] which when used to diagnose the disease early can result in significantly reduced morbidity [9].

In a predisposed individual, angioinvasive nature of fungal elements leads to thrombosis and necrotizing vasculitis resulting in tissue infarction.[10] Infarction with suppuration is one of the key histological findings in AIFS [11]. This reflects on imaging as loss of contrast enhancement (LoCE) involving one or more sites: wall of nasal cavity including septum and turbinates, paranasal sinus walls, extrasinosal soft tissues including pterygopalatine fossa, masticator and visceral spaces of the neck, skull base and intracranial soft tissue [12]. Due to its superior soft tissue contrast resolution or ability to detect subtle differences in tissues of similar appearance, MRI is better at identifying extrasinosal soft tissue involvement [13] and LoCE leading to higher sensitivity of MRI when compared to CT for diagnosis of AIFS [14, 15].

Higher survival rates are noted in patients diagnosed promptly with timely imaging.[16] Radiologists must identify the presence and extent of LoCE at diagnosis; mapping of this necrotic or devitalized tissue that needs complete surgical debridement is vital as it is an independent poor prognostic factor for disease specific mortality [17]. Presence of any remnant LoCE lesions after surgical debridement also adversely affects the survival [18]. With this background, in our institute, we prefer MRI with contrast (unless contraindicated) over CT for suspected AIFS patients due to its ability to exclude diagnosis and also due its superiority in identifying LoCE lesions. In our study, both the MRI parameters (LoCE and extrasinosal involvement) had similar sensitivity while the earlier literature showed extrasinosal involvement to be a more sensitive MRI parameter [14]. One possible explanation for increased frequency of LoCE in our study could be due to presentation to the hospital at a more advanced stage of the disease, partly contributed by lack of availability of in-patient beds owing to the ongoing second wave of COVID-19 pandemic during the study period. We believe that some of the key reasons for substantially higher interobserver agreement between the two radiologists in our study across all the imaging findings compared to other studies [14]. are standardization of imaging protocol and uniformity in interpreting the MR images as a part of the initiative undertaken at our institutional level in preparation for this AIFS epidemic. This helped us overcome the barrier of potentially different thresholds between observers for identifying various imaging findings, especially LoCE [14]. It is important to understand that PPV and NPV depend on the prevalence of disease being tested [19] and as the prevalence of COVID-19 associated AIFS has not been taken into account in our study, the PPV and NPV values may be spuriously high or low.

One of the key highlights of our study is the relatively larger number of 'cases' compared to any other single centre

original research articles published in literature on COVID-19 associated AIFS [1,20–24]. All patients were treated with surgical debridement and antifungal medications except for patients with persistent SARS CoV2 RT-PCR positive swab, who received antifungal therapy alone.

Table 1: Demographic, comorbidity and key imaging data

Variable	Total	AFIS	Controls
No. of patients	91	68	23
Median age (range) in years	54(24-84)	54 (24-79)	54(27-84)
Gender			
-Male	67 (73.6%)	51 (75%)	16 (69.6%)
-Female	24 (26.4%)	17 (25%)	7 (30.4%)
Diabetes	45	41	4
Concurrent or recent COVID-19 infection	91	68	23
MRI specification			
-Non-contrast	7	3	4
-With contrast	84	65	19
Key Imaging findings			
-LoCE (turbinates, nasal septum or paranasal sinus wall) (N=65)[a]		60 (92%)	0
-Extrasinosal involvement (N=68)		62 (91%)	0
-Orbital involvement (N=68)		49 (72%)	0
-Cavernous sinus involvement (N=68)		22 (32%)	0
-Intracranial involvement (N=68)		19 (28%)	0
-Major vascular involvement (N=68)		6 (9%)	0

[a]LoCE could not be assessed in 3 patients who had non-contrast MRI.

Table 2: Interobserver agreement between Radiologists

Parameter	k value (95% CI)	Strength of agreement	p Value
Diagnosis (definite AIFS Vs Possible AIFS Vs non-fungal)	0.881 (0.784-0.977)	Almost perfect	<0.001
LoCE of nasal turbinates	0.956 (0.895-1.016)	Almost perfect	<0.001
LoCE of nasal septum	0.884 (0.818-1.013)	Almost perfect	<0.001
LoCE paranasal sinus wall	0.976 (0.928-1.023)	Almost perfect	<0.001
Extrasinosal soft tissue involvement (excluding orbits)	0.925 (0.84-1.009)	Almost perfect	<0.001
Pterygopalatine fossa involvement	0.842 (0.73-0.953)	Almost perfect	<0.001
Orbital cellulitis	0.956 (0.895-1.016)	Almost perfect	<0.001
Orbital apex involvement	0.947 (0.874-1.019)	Almost perfect	<0.001
Optic nerve / nerve sheath involvement	0.938 (0.853-1.022)	Almost perfect	<0.001
Cavernous sinus involvement	0.907 (0.82-0.993)	Almost perfect	<0.001
Extra-axial involvement (meningitis/fluid collection)	0.966 (0.899-1.032)	Almost perfect	<0.001
Intra-axial involvement (cerebritis/perineural spread/abscess)	0.904 (0.772-1.035)	Almost perfect	<0.001
Major vascular involvement (thrombosis/vasculitis)	0.903 (0.714-1.091)	Almost perfect	<0.001

k = Cohen's kappa statistic
< 0.00 = less than chance agreement/poor
0.01-0.20 = slight agreement
0.21-0.40 = fair agreement
0.41-0.60 = moderate agreement
0.61-0.80 = substantial agreement
0.81-0.99 = almost perfect agreement

Table 3: Sensitivity, Specificity, PPV, NPV and accuracy of MRI for Radiologist 1 (TP) and Radiologist 2 (SG)

		LoCE	Extrasinosal involvement	MRI diagnosis: Definite AIFS
Sensitivity	Radiologist 1	89%	91%	93%
	Radiologist 2	92%	90%	91%
Specificity	Radiologist 1	100%	100%	100%
	Radiologist 2	100%	100%	100%
PPV	Radiologist 1	100%	100%	100%
	Radiologist 2	100%	100%	100%
NPV	Radiologist 1	72%	78%	82%
	Radiologist 2	80%	77%	79%
Accuracy	Radiologist 1	92%	93%	94%
	Radiologist 2	94%	92%	93%

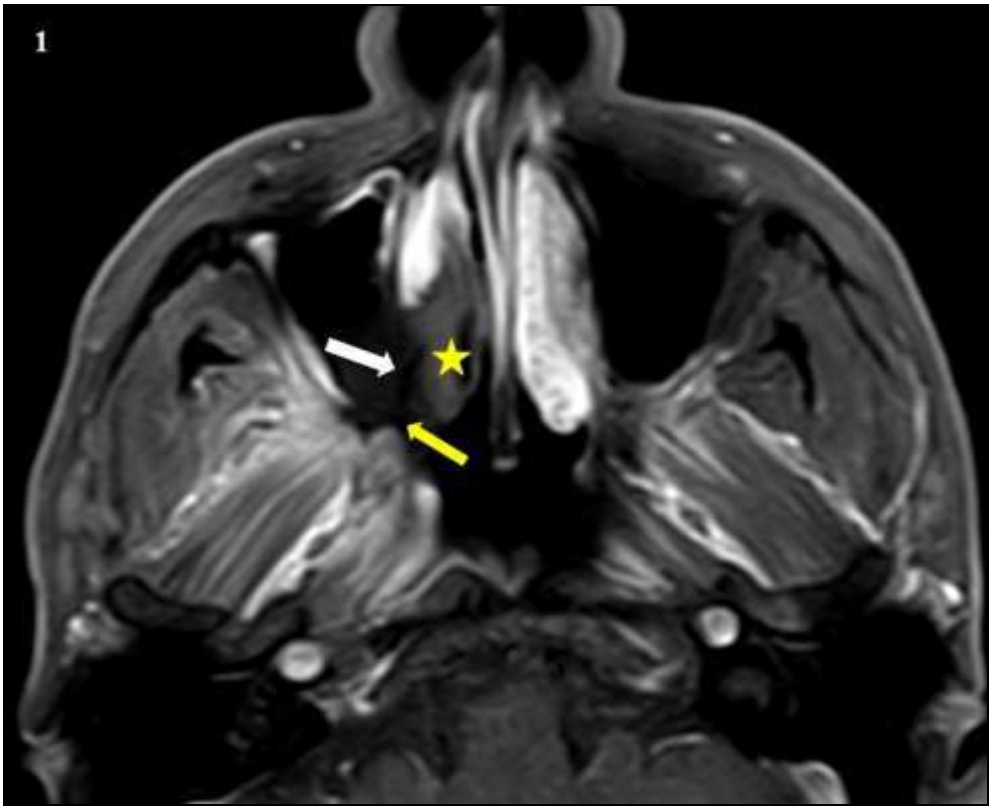


Fig 1: 49 year old man with acute invasive fungal sinusitis. T1 weighted post contrast axial MR image showing partially non-enhancing right inferior nasal turbinate (yellow asterisk), adjacent right maxillary sinus wall (white arrow) and pterygoid bone (yellow arrow), suggestive of necrosis

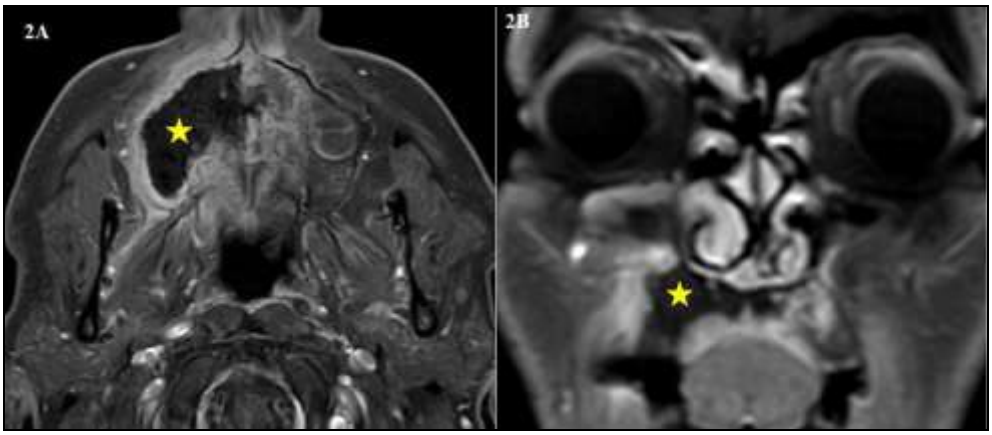


Fig 2: 58 year old man with acute invasive fungal sinusitis. T1 weighted post contrast axial and coronal MR images showing loss of contrast enhancement suggestive of necrosis in the right half of hard palate & alveolar process (yellow asterisks)

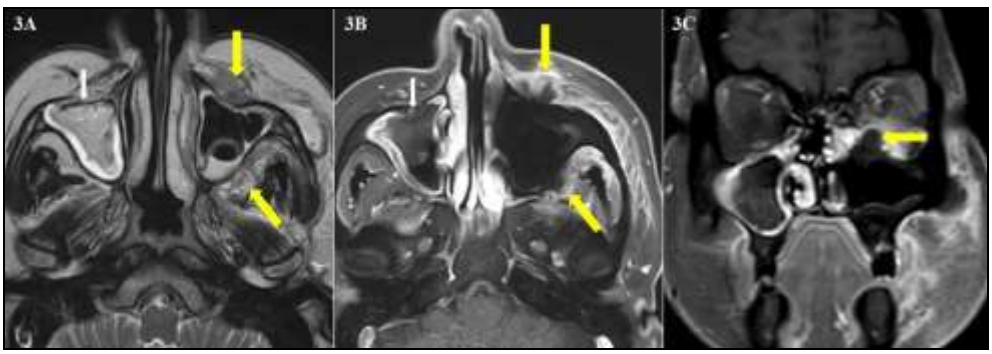


Fig 3: 57 year old woman with acute invasive fungal sinusitis. T2 weighted axial MR image (3A), T1 weighted post contrast axial and coronal MR images (3B and 3C) showing thin T2 hypointense linear area along the anterior wall of right maxillary sinus (white arrow in 3A) with corresponding area of necrosis (white arrow in 3B), completely non-enhancing left maxillary sinus walls (3B and 3C) suggestive of necrosis, associated pre-antral and retro-antral abscesses (yellow arrows in 3A and 3B) and left orbital abscess (yellow arrow in 3C)

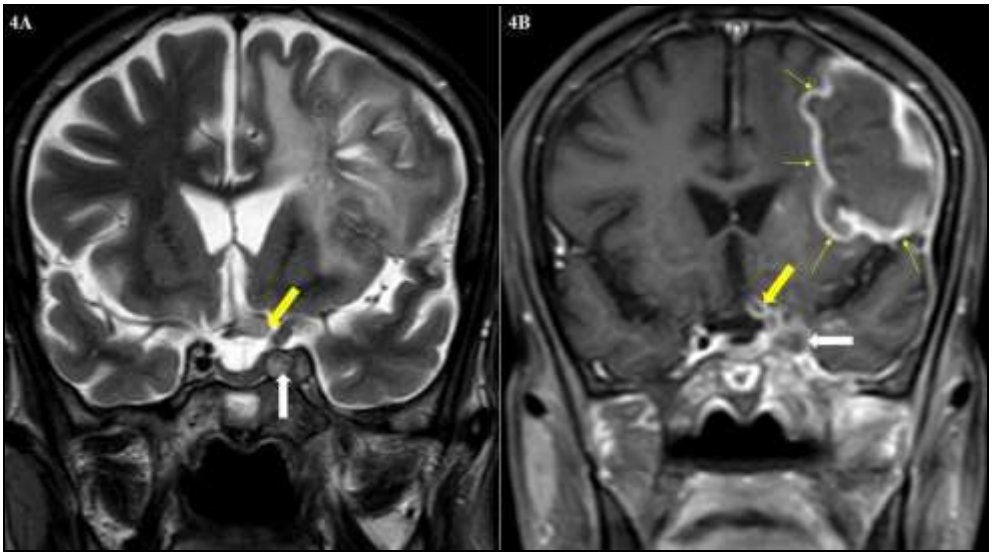


Fig 4: 48 year old man with acute invasive fungal sinusitis with orbital cellulitis (not shown in image) and intracranial abscess. T2 weighted coronal MR image (4A) and T1 weighted post contrast coronal MR image (4B) showing left frontal lobe abscess (thin yellow arrows in 4B), left optic neuritis (solid yellow arrows in 4A and 4B), non-enhancing left cavernous sinus (solid white arrow in 4B) suggestive of cavernous sinus thrombosis and loss of flow void of left cavernous segment of ICA (solid white arrow in 4A) suggestive of left ICA thrombosis

5. Conclusion

Contrast MRI of paranasal sinuses is a highly sensitive and specific modality to diagnose AIFS with excellent interobserver agreement. Loss of contrast enhancement and extrasinosal involvement are two highly reliable MRI parameters in suggesting the diagnosis and in guiding extent of surgical debridement.

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