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The Insular Knife-Cut Sign: A Novel Imaging Marker In The Evaluation Of Paediatric Herpes Simplex Virus Encephalitis

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Abstract

Background: Herpes simplex virus encephalitis (HSVE) is the most common cause of sporadic, non-epidemic viral encephalitis worldwide and an important cause of acute encephalopathy in children. The "insular knife-cut" sign — a sharp demarcation between FLAIR-hyperintense insular cortex and the adjacent basal ganglia — has recently been proposed as a specific MRI marker of HSVE, but paediatric data, particularly from India, remain scarce.

Objective: To assess the frequency and diagnostic performance of the insular knife-cut sign in differentiating paediatric HSVE from other causes of encephalitis.

Methods: This single-centre, retrospective study reviewed brain MRI of 20 children (<18 years) with suspected encephalitis performed within seven days of onset, between January and October 2025, at a tertiary hospital in Karnataka. Patients were grouped as HSV-positive (n = 6) or other encephalitis (n = 14) by clinical, CSF, PCR, and consensus criteria. The insular knife-cut sign and other MRI features were recorded and diagnostic performance calculated.

Results: The mean age was 8.5 years, with an equal male-to-female ratio. The insular knife-cut sign was identified in 4 of 6 (66.7%) HSV-positive patients and in none of the 14 alternative-diagnosis patients, giving a sensitivity of 66.7%, specificity of 100%, PPV of 100%, and NPV of 87.5%.

Conclusion: The insular knife-cut sign is an early, highly specific MRI finding that strongly supports a diagnosis of HSVE in children with new-onset encephalitis. Its detection should prompt immediate empirical antiviral therapy even while confirmatory virological results are awaited.

Keywords: Herpes simplex encephalitis; insular knife-cut sign; magnetic resonance imaging; paediatric encephalitis; FLAIR imaging

Introduction

Herpes simplex virus encephalitis (HSVE) is widely regarded as the most common identifiable cause of sporadic, non-epidemic viral encephalitis in children and adults worldwide, and remains a leading cause of severe acute encephalopathy despite the availability of effective antiviral therapy.[1] Population-based surveillance from Europe and elsewhere has consistently identified herpes simplex virus among the leading agents recovered in patients with acute infectious encephalitis, contributing disproportionately to morbidity and mortality relative to its overall incidence.[2,3] Children and adolescents are not spared: large case series indicate that this age group accounts for close to one-third of all reported

HSVE cases, frequently with presentations that are less specific than those typically described in adults.[4]

Clinically, HSVE typically presents with fever, headache, behavioural change, focal neurological deficits, seizures, or altered mental status, and the illness can progress rapidly over a period of days.[1] Because these clinical features overlap extensively with those of autoimmune encephalitis, metabolic encephalopathies, and other infectious causes, neuroimaging plays a central role in the early diagnostic pathway. [5] On magnetic resonance imaging, HSVE classically manifests as asymmetric T2/FLAIR hyperintensity involving the temporal poles, mesial temporal structures, and insular cortex, frequently accompanied by restricted diffusion on diffusion-weighted imaging (DWI) sequences.[6,7]

Cerebrospinal fluid (CSF) pleocytosis and epileptiform discharges on electroencephalography are common accompaniments of HSVE but are nonspecific, overlapping considerably with autoimmune encephalitis, structural epilepsy, and other infectious or inflammatory encephalopathies. This diagnostic overlap carries real clinical consequences, since mortality and long-term neurological morbidity rise sharply when empirical acyclovir therapy is deferred pending confirmatory virological testing.[1] Reliable imaging clues that can be recognised on the first MRI, before CSF polymerase chain reaction (PCR) results become available, are therefore of substantial clinical value, particularly in resource-limited settings where PCR turnaround may extend well beyond 24–48 hours.

Against this background, a sharp linear demarcation between FLAIR-hyperintense insular cortex and the adjacent basal ganglia, running along the course of the external capsule, has recently been described and termed the "insular knife-cut" sign. In the largest multicentre validation cohort published to date, this sign was identified in just over half of confirmed HSVE cases but in fewer than 1% of patients with alternative diagnoses, corresponding to a specificity exceeding 99%.[11] The sign is conceptually attractive because the insula and basal ganglia, although anatomically contiguous, are separated by the external capsule and claustrum — a watershed-like boundary that appears to restrict the spread of HSV-related cytotoxic and vasogenic oedema, in contrast to many of its mimics, in which abnormal signal more often extends across this boundary into the deep grey matter.[12]

Most published data on the insular knife-cut sign derive from adult, predominantly European, cohorts, and corroborative paediatric evidence — particularly from the Indian subcontinent, where the burden of acute encephalitis syndrome in children remains substantial — is limited. The present study was therefore undertaken to evaluate the frequency of the insular knife-cut sign in a paediatric population with suspected encephalitis and to determine its diagnostic performance in distinguishing HSVE from other encephalitis aetiologies, including autoimmune encephalitis, metabolic disorders, and epilepsy-related imaging change.

2. Objectives

1. To assess the diagnostic utility of the insular knife-cut sign in differentiating paediatric HSVE from other causes of encephalitis, including autoimmune encephalitis, metabolic disorders, and epilepsy-related changes.
2. To evaluate the diagnostic performance — sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) — of the insular knife-cut sign in differentiating HSVE from other encephalitides.

3. Materials And Methods

3.1 Study Design and Setting

This was a single-centre, hospital-based, retrospective study conducted in the Department of Radiodiagnosis, J.J.M. Medical College, Davangere, Karnataka, India. The study included children younger than 18 years who underwent brain MRI for suspected encephalitis between January 2025 and October 2025. Institutional Human Ethics Committee approval was obtained prior to data collection.

3.2 Study Population

A total of 20 children met the inclusion criteria. Inclusion criteria were: patients who underwent brain MRI for suspected encephalitis; MRI performed within the acute stage, defined as within seven days of symptom onset; and a confirmed final diagnosis established on the basis of clinical findings, CSF analysis, PCR results, or multidisciplinary consensus. Patients were excluded if brain MRI was of poor diagnostic quality because of motion artefact, if CSF

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analysis was unavailable, or if imaging was obtained during the chronic or post-encephalitic sequelae stage of illness.

On the basis of the final clinical-virological diagnosis, patients were divided into two groups: HSV-positive encephalitis (n = 6) and other encephalitis aetiologies (n = 14), the latter comprising children with autoimmune encephalitis, presumed viral encephalitis of non-HSV origin, and encephalopathy of uncertain aetiology (Table 1).

3.3 MRI Protocol

All examinations were performed on a 1.5-Tesla MRI scanner. The imaging protocol included T1-weighted, T2-weighted, FLAIR, diffusion-weighted imaging with apparent diffusion coefficient (ADC) mapping, gradient-recalled echo (GRE) or susceptibility-weighted imaging, and post-contrast T1-weighted sequences. Two radiologists, blinded to the final clinical diagnosis, independently reviewed all axial FLAIR images for the presence or absence of the insular knife-cut sign, defined as a sharp, linear demarcation along the external capsule between FLAIR-hyperintense insular cortical-subcortical abnormality and the adjacent basal ganglia. Discrepancies were resolved by consensus. The presence of temporal pole FLAIR hyperintensity, insular involvement of any type, diffusion restriction, and basal ganglia involvement were also recorded for each patient.

3.4 Statistical Analysis

Descriptive statistics (mean, proportions) were used to summarise demographic and imaging variables. The presence of the insular knife-cut sign and other MRI features was tabulated against the final diagnostic group (HSV-positive versus other encephalitis) using 2×2 contingency tables, from which sensitivity, specificity, PPV, and NPV of the insular knife-cut sign for the diagnosis of HSVE were calculated using standard formulae.

4. Results

4.1 Demographic and Clinical Profile

Twenty children with suspected encephalitis were included in the study (Table 1). The mean age of the cohort was 8.5 years, with an equal male-to-female ratio of 1:1. Six children (30.0%) had HSV-positive encephalitis confirmed by CSF PCR, clinical features, or multidisciplinary consensus, while the remaining 14 children (70.0%) had encephalitis attributable to other aetiologies.

Table 1. Demographic profile and group distribution of the study population (n = 20).

Parameter	Value
Total number of patients	20
Mean age (years)	8.5
Sex ratio (M:F)	1:1
HSV-positive encephalitis, n (%)	6 (30.0)
Other encephalitis aetiologies, n (%)	14 (70.0)

4.2 Comparison of MRI Features

The insular knife-cut sign was identified on the initial brain MRI in 4 of 6 (66.7%) children with HSV-positive encephalitis, compared with none of the 14 children (0%) with alternative diagnoses (Table 2). Temporal pole FLAIR hyperintensity was present in all six (100%) HSVE patients but in only 4 of 14 (28.6%) patients with other encephalitis aetiologies. Insular involvement of any type — with or without a clearly demarcated knife-cut

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appearance — was seen in all six (100%) HSVE patients and in 5 of 14 (35.7%) patients with other diagnoses. Diffusion restriction was present in 5 of 6 (83.3%) HSVE patients and in 6 of 14 (42.8%) patients with other diagnoses, while basal ganglia involvement, characteristically absent in HSVE, was noted in 3 of 14 (21.4%) patients with alternative diagnoses and in none of the HSVE patients.

Table 2. Comparison of MRI features between the HSV-positive and other encephalitis groups.

MRI Feature	HSV Encephalitis (n = 6)	Other Encephalitis (n = 14)
Insular knife-cut sign	4 (66.7%)	0 (0%)
Temporal pole FLAIR hyperintensity	6 (100%)	4 (28.6%)
Insular involvement (any type)	6 (100%)	5 (35.7%)
Diffusion restriction	5 (83.3%)	6 (42.8%)
Basal ganglia involvement	0 (0%)	3 (21.4%)

4.3 Diagnostic Performance of the Insular Knife-Cut Sign

Using the final clinical-virological diagnosis as the reference standard, the insular knife-cut sign demonstrated a sensitivity of 66.7%, specificity of 100%, PPV of 100%, and NPV of 87.5% for the diagnosis of HSVE in this paediatric cohort (Table 3). The sign was, therefore, highly specific — its presence on the initial MRI was never observed in a child with a non-HSV diagnosis — while its sensitivity was moderate, indicating that its absence on a single MRI study does not reliably exclude HSVE.

Table 3. Diagnostic Performance Of The Insular Knife-Cut Sign For HSV Encephalitis.

Diagnostic Metric	Value
Sensitivity	66.7%
Specificity	100%
Positive predictive value (PPV)	100%
Negative predictive value (NPV)	87.5%

4.4 Illustrative Cases

Case 1: A 9-year-old boy presented with fever, behavioural change, and new-onset focal seizures. Brain MRI performed in the acute stage demonstrated T2/FLAIR hyperintensity involving the right insular cortex with a sharp, linear demarcation from the adjacent basal ganglia along the external capsule, in keeping with the insular knife-cut sign. No foci of susceptibility blooming and no diffusion restriction were identified (Figure 1). CSF PCR subsequently confirmed HSV-1 infection, and the child was started on intravenous acyclovir.

Figure 1. Case 1 (9-year-old boy). Axial (A) DWI and (B) ADC images show no definite diffusion restriction within the right insula. Axial (C) and (D) T2/FLAIR images demonstrate hyperintensity in the

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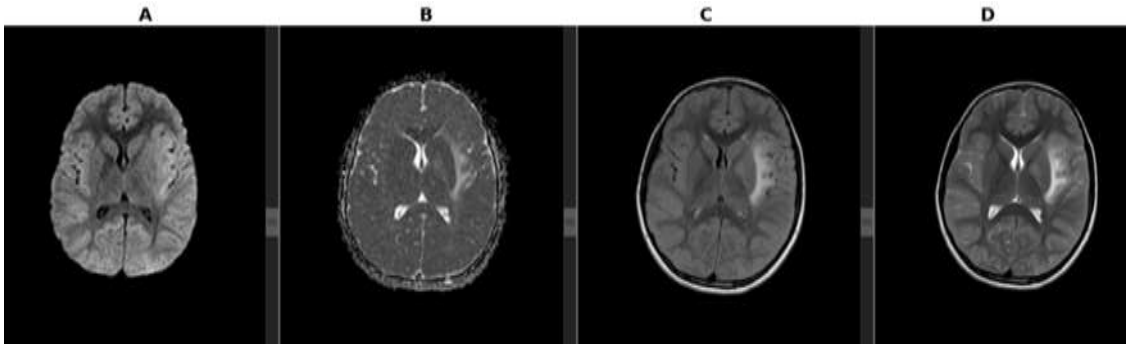
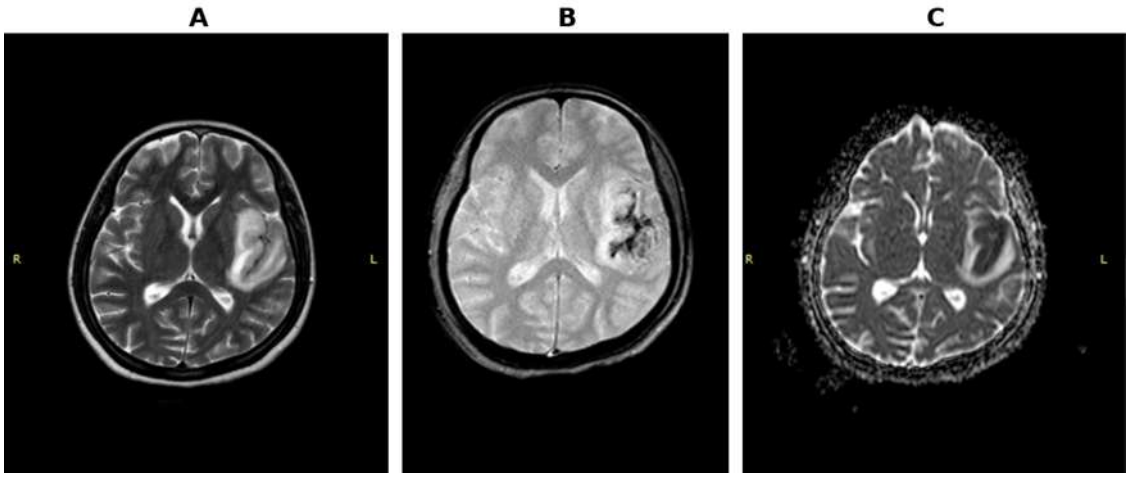
right insular cortex with a sharp, linear demarcation from the basal ganglia along the external capsule (D) — the insular knife-cut sign — without accompanying blooming or restricted diffusion.



Case 2: A 14-year-old girl presented with fever, altered sensorium, and right-sided focal seizures. Brain MRI demonstrated T2/FLAIR hyperintensity in the left insular cortex with sharp demarcation from the basal ganglia, again consistent with the insular knife-cut sign. In contrast to Case 1, this patient additionally showed areas of true diffusion restriction and small foci of susceptibility blooming within the affected insular cortex, reflecting cytotoxic oedema and microhaemorrhage, respectively (Figure 2). CSF PCR confirmed HSV-1 encephalitis.

Figure 2. Case 2 (14-year-old girl). (A) Axial T2/FLAIR image shows hyperintensity in the left insular cortex with sharp demarcation from the basal ganglia — the insular knife-cut sign. (B) Axial GRE image demonstrates foci of blooming within the lesion, indicating microhaemorrhage. (C) Axial DWI image shows corresponding hyperintensity in the left insula, consistent with true diffusion restriction.



4.5 Comparison With Published Literature

Table 4 compares the diagnostic performance of the insular knife-cut sign observed in the present paediatric cohort with that reported in the largest published validation series to date.[11] The substantially higher sensitivity observed in our cohort should be interpreted in light of the very small number of HSVE patients (n = 6) and the inherent imprecision of diagnostic estimates derived from small samples; nonetheless, the finding of 100% specificity in both studies, despite differences in age group, geography, and sample size, lends weight to the reproducibility of the sign as a highly specific — if only moderately sensitive — marker of HSVE.

Table 4. Comparison of the present study findings with the largest published validation series on the insular knife-cut sign.

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Study	Population	HSVE / Total (n)	Sensitivity	Specificity
Marini et al.[11] (2025)	Adult, multicentre (Italy)	44 / 188	52.3%	99.3%
Present study (2026)	Paediatric, single-centre (India)	6 / 20	66.7%	100%

5. Discussion

In this retrospective paediatric cohort, the insular knife-cut sign was found in two-thirds of children with confirmed HSV-positive encephalitis and in none of the children with alternative diagnoses, yielding a specificity of 100% and a sensitivity of 66.7%. These findings are broadly consistent with, and in fact more favourable than, those reported by Marini et al. in the largest validation cohort published to date, in which the sign was present in 52.3% of HSVE patients and in only 0.7% of patients with alternative diagnoses, corresponding to a specificity of 99.3% and a sensitivity of 52.3% on the initial MRI.[11] Taken together, these two studies — performed on different continents, in different age groups, and in different healthcare settings — support the insular knife-cut sign as a reproducible and highly specific, if moderately sensitive, early radiological marker of HSVE.

The anatomical basis for the sign lies in the relative resistance of the basal ganglia to HSV-related injury. HSV preferentially involves the limbic system, mesial temporal structures, and insular cortex through patterns of viral spread along olfactory and trigeminal pathways, while the basal ganglia, supplied by a largely separate vascular and connective architecture and physically separated from the insula by the external capsule and claustrum, are typically spared.[1,6] This produces the sharp "knife-cut" interface that is far less commonly observed in the diffuse or patchy insular involvement seen in autoimmune limbic encephalitis, metabolic encephalopathies, or seizure-related peri-ictal change, in which abnormal signal more often blurs across the insular-basal ganglia boundary or, conversely, predominantly affects the basal ganglia themselves.[8]

Sensitivity in the present study, as in the Italian validation series, was only moderate. Two of the six HSVE patients in our cohort did not demonstrate the sign on initial imaging. A plausible explanation, consistent with prior literature, is that imaging performed very early in the disease course may precede the development of full-thickness insular involvement required to produce a clearly demarcated boundary; partial insular involvement that does not extend to the full insular ribbon may likewise fail to meet strict criteria for the sign.[11] This observation has practical implications: a negative initial MRI should not be used to exclude HSVE in a clinically compatible patient, and repeat imaging after 24–48 hours may unmask the sign as the disease evolves, a phenomenon also documented in larger adult cohorts in which sensitivity rose substantially when both initial and follow-up MRIs were considered.[11]

The two illustrative cases in this series highlight the spectrum of imaging findings that may accompany the insular knife-cut sign. In Case 1, the sign was identified in isolation, without accompanying diffusion restriction or susceptibility blooming, illustrating that the sign itself, rather than these accessory findings, carried diagnostic weight. In Case 2, the additional presence of true diffusion restriction and micro haemorrhagic blooming is consistent with the comparative imaging literature, which describes restricted diffusion in the majority of HSVE cases and haemorrhagic transformation as a recognised, if less consistent, feature of more advanced disease.[7]

The clinical importance of recognising the insular knife-cut sign lies chiefly in its potential to expedite empirical antiviral therapy. Guideline bodies, including the Infectious Diseases Society of America and the Association of British Neurologists, emphasise that empirical intravenous acyclovir should be started immediately in any patient with suspected

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encephalitis, without waiting for CSF PCR confirmation, given that even short delays beyond 24–48 hours have been independently associated with worse neurological outcomes.[1],[9],[10] Paediatric-specific guidance reinforces this point, given that diagnostic delay and atypical presentation are more common in children than in adults.[13] A reliable imaging sign that can be recognised on a single MRI sequence at the bedside, well before CSF PCR results return, therefore has the potential to meaningfully shorten time to treatment in real-world practice, particularly in resource-limited settings.

Differentiating HSVE from its mimics on imaging remains clinically important, since several other entities can produce temporal and insular signal change that superficially resembles HSVE. Autoimmune and paraneoplastic limbic encephalitis, in particular, can closely mimic the temporal-insular distribution of HSVE but typically lack the sharp basal ganglia demarcation and instead show more symmetric, bilateral mesial temporal involvement without extension along a discrete external capsule boundary.[8] Less commonly, infectious mimics such as neurosyphilis have been reported to produce an imaging pattern indistinguishable from HSVE, including a similar mesiotemporal and insular "knife-cut"-like appearance, underscoring that this sign, while highly specific for HSVE in the populations studied so far, is not entirely pathognomonic and should always be interpreted alongside clinical and CSF findings.[14],[15] A systematic comparison of temporal lobe encephalitis aetiologies similarly found that, while imaging features can help discriminate HSVE from its mimics, no single sign is infallible, and a combination of clinical, CSF, and imaging clues performs best.[12]

This study has several limitations. The sample size was small, particularly the HSV-positive group (n = 6), which limits the precision of the sensitivity and NPV estimates and precludes meaningful subgroup or multivariate analysis. The retrospective, single-centre design may introduce selection bias, and the absence of routine follow-up MRI in patients with an initially negative scan may have underestimated the true sensitivity of the sign, as discussed above. Long-term neurological outcomes were not assessed. Despite these limitations, the findings reinforce, in an Indian paediatric population, the diagnostic value of a sign first described in adult European cohorts, and add to the small but growing body of evidence supporting its cross-population reproducibility.

6. Conclusion

The insular knife-cut sign is an early and highly specific MRI finding that is frequently, though not invariably, detected in children with HSV encephalitis. Its detection in a child with new-onset encephalitis should raise strong suspicion for HSVE and support, rather than replace, clinical decision-making regarding empirical antiviral therapy, particularly while confirmatory CSF PCR results are pending. Conversely, its absence on a single MRI does not exclude the diagnosis, and repeat imaging should be considered when clinical suspicion remains high. This study validates the diagnostic utility of the insular knife-cut sign in a paediatric Indian population and supports its incorporation, alongside clinical and CSF parameters, into the early diagnostic assessment of children with suspected encephalitis.

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