A Pediatric Case of Late Relapse of Neonatal Herpes Simplex Encephalitis in a 14-Year-Old

Kevin Jiang[1]*, Sally Choi[1], Carlos Bazan[1], Andrea Gilbert[2], Jason Lally[1]

[1]*UT Health San Antonio, Department of Radiology, San Antonio, USA*
[2]*UT Health San Antonio, Department of Pathology, San Antonio, USA*

***Correspondence:** Kevin Jiang, MD, UT Health San Antonio, Department of Radiology, 7703 Floyd Curl Drive – MC 7800, San Antonio, TX 78229-3900, USA

jiangk@uthscsa.edu

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Authors' Contributions
All authors stated above made substantial contributions to the conception and design of this case report. All authors participated in the draft and revision process that yielded the final manuscript.

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None

Consent
No

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N/A

ABSTRACT

Herpes simplex encephalitis is the most common type of viral encephalitis. However, recurrence or relapse is rare. Late relapse, defined as recurrent active infection later than 3 months from the end of antiviral treatment, is even rarer. The following case illustrates the longest recorded idiopathic late relapse of herpes simplex encephalitis with biopsy-proven confirmation on histopathology. The literature suggests multiple mechanisms for relapse including latent reactivation, post-infectious autoimmune disease, and genetic predisposition. Regardless, untreated recurrent herpes simplex encephalitis has a high morbidity and mortality, and it is the only etiology of viral encephalitis with an effective anti-viral treatment. As such, it should remain an important consideration on the differential diagnosis of encephalitis for prompt recognition and timely management.

CASE REPORT

CASE REPORT

A 14-year-old female with history of neonatal encephalitis and multiple other medical co-morbidities including global developmental delay, intractable epilepsy, spastic cerebral palsy, and obstructive sleep apnea presented with breakthrough seizures and altered level of consciousness.

Imaging Findings

Prior to her acute presentation, comparison MRI brain examinations showed multifocal encephalomalacia and volume loss representing chronic sequela of remote neonatal herpes encephalitis. No abnormal edema or enhancement was present. At the acute presentation, repeat MRI brain with and without contrast exam showed a new peripherally enhancing cystic lesion in the right parietal lobe. Additionally, there was new brain parenchymal edema on T2/FLAIR with nodular and gyriform enhancement of scattered cerebral cortex, deep subcortical gray matter nuclei, and brainstem, suggesting underlying pathologic process with acute inflammation and brain swelling.

Pathology Findings

Tissue sample of “right frontal mass” brain biopsy yielded pathology findings of Herpes Simplex Encephalitis. Cowdry type A inclusions, which are typical of acute phase, and perivascular

and intraparenchymal lymphocytic infiltrates, which are typical in chronic phase of herpes simplex encephalitis, were both seen. The combination of these supported a recurrent or acute on chronic herpes encephalitis.

Management

Aside from an elevated temperature from the patient's baseline (36.1 C) and mild leukocytosis of 15.4 x 10^3, an initial extensive workup was unremarkable. Specifically, a lumbar puncture was performed, and cerebrospinal fluid testing was negative for HSV-1/2 PCR and other encephalitides. Due to clinical deterioration, stereotactic biopsy of the right parietal cystic lesion was pursued and yielded histopathological findings compatible with a recurrent herpes simplex encephalitis. The patient was subsequently treated with a 21-day regimen of acyclovir and discharged on a daily prescription of valacyclovir.

Follow-up

Since this hospitalization, the patient has had multiple hospital admissions related to her complex medical condition. She has had no reported breakthrough seizures on her current anti-epileptic regimen of 1500 mg BID of Keppra. Unfortunately, the patient's overall prognosis is poor as she is currently in hospice.

DISCUSSION

Etiology & demographics

Herpes simplex encephalitis is by far the most common identifiable cause of viral encephalitis, ranging from 10-40% of all cases [1-3]. Recurrent herpes simplex encephalitis is uncommon with studies reporting incidences of 5-26%, most of which occur in less than 3 months after antiviral treatment [4,5]. To our knowledge, the data on late relapse of herpes simplex encephalitis, defined as longer than 3 months after antiviral treatment, is limited with only 27 documented cases [6-27]. Among these, there was a slightly greater prevalence among females (12/22), and most were pediatric patients (19/27).

The prevailing hypothesis for the etiology of relapse is reactivation of latent virus [15, 20]. This has been demonstrated either through the detection of herpes simplex virus in cerebrospinal fluid/brain tissue or imaging findings of new herpetic lesions superimposed on old ones, all of which imply viral reactivation. The most common identifiable trigger for reactivation has been attributed to surgical manipulation of infected brain parenchyma, comprising 12 of the cases [27]. Pharmacologic-induced immunosuppression has also been found to be a contributing factor in one case of corticotropin treatment of infantile spasms and another case of carbamazepine induced hypogammaglobulinemia [12,14]. Other proposed mechanisms of relapse include postinfectious autoimmune disease and genetic predisposition [9,28]. For the current case presented in this report, reactivation of latent virus was the most likely contributing cause, as there were pathologic and imaging findings correlating with the clinical presentation. No obvious trigger could be identified. This case is unique in that it represents the longest documented idiopathic relapse (over 13 years) of herpes simplex encephalitis in a pediatric patient, with the previous longest being 8.5 years [15].

Clinical and imaging findings

Clinical presentation and imaging findings of relapsed herpes simplex encephalitis are indistinguishable from primary infection [6-27]. Fever is the most common reported presenting symptom (21/27), followed by seizures (12/27), both of which our patient endorsed. Other reported symptoms include headache, aphasia, consciousness disturbance, drowsiness, and lethargy, as is expected with neurologic dysfunction secondary to cerebral insult.

The only imaging finding specific to relapse is new herpetic lesions superimposed on old lesions. Otherwise, the findings are nonspecific and characteristic of encephalitis in general. These findings on MRI include symmetric or asymmetric T2/FLAIR hyperintensity and gyral enhancement in the temporal lobes sparing the basal ganglia [29]. Extralimbic involvement is more common in children than adults, most commonly in the parietal lobes but may involve any lobes' cortical and white matter [30]. CT appearance is often normal, though may display subtle hypodensity of affected areas.

Treatment & prognosis

Herpes simplex encephalitis is the only viral encephalitis with an effective antiviral treatment, and relapses have the same management. Most studies reported a 21-day regimen of intravenous acyclovir, though some clinicians employed longer treatment duration [7,8,10,12,23,25,27]. Some studies added corticosteroid treatment [9,10,27]. Intravenous immunoglobulin therapy was specifically used in the case of carbamazepine-induced hypogammaglobinemia [14]. Some studies advocated for the use of prophylactic acyclovir in all patients undergoing neurosurgery with a known history of herpes simplex encephalitis [18,21-24,26].

Prognosis seems to be related to both the extent of relapse symptoms at the time acyclovir was initiated and the pre-existing complex medical condition as a result of the primary infection. Timely initiation of acyclovir treatment is associated with the best outcomes. The most common outcome is varying degrees (predominantly mild) of persistent neurological deterioration from baseline. Two cases suggest this may be due to incomplete treatment of the primary infection [6,10]. Complete return to baseline is documented in seven cases [11,16,18,19,21,23,27]. However, there are also two reported cases of death [15,17].

Differential diagnosis

The differential diagnosis for this entity includes autoimmune limbic encephalitis, diffuse low-grade astrocytoma, Mollaret's meningitis, and stroke.

Autoimmune limbic encephalitis has many similar imaging findings to recurrent HSV encephalitis, including often asymmetric cortical T2/FLAIR hyperintensity of the mesial temporal lobes and limbic systems. In autoimmune limbic encephalitis, the lateral temporal lobe and insular lobes are less commonly involved, and the basal ganglia is frequently involved [31], as opposed to in recurrent HSV encephalitis, which typically spares the basal ganglia and often involves the diffuse temporal and insular cortices. CT appearance is often normal. Antibody testing and clinical history will assist in differentiating between these diagnoses.

Diffuse low-grade astrocytoma demonstrates T2 hyperintensity primarily involving the supratentorial white matter. A couple imaging features of diffuse astrocytoma that differentiate it from recurrent HSV encephalitis include suppressed T2 signal on FLAIR sequence representing T2/FLAIR mismatch sign, which is highly specific for IDH-mutant astrocytomas, as well as expansion of affected brain parenchyma [29,32]. CT appearance may also demonstrate iso/hypodense regions of parenchymal expansion and mass effect.

Middle cerebral artery (MCA) stroke can have similar presentation and imaging findings as herpes simplex encephalitis, likely due to similar predilections for the temporal lobe. Clinical presentation of MCA stroke includes acute neurologic deficit, and imaging findings include nonspecific CT hypoattenuation of the affected region. CT angiography can be helpful for diagnosing stroke if a vascular etiology is identified such as an embolus or stenosis. MR may have more specific findings related to encephalitis, though T2/FLAIR hyperintensities and restricted diffusion which may incidentally follow a vascular distribution can be indistinguishable from stroke. A differentiating imaging characteristic is that an MCA artery stroke can involve the basal ganglia, which are typically spared in herpes simplex encephalitis. In severe herpes simplex encephalitis, however, the basal ganglia structures can also be involved. Ultimately, diagnosis is made by a combination of early MRI imaging and CSF testing [33-35].

Mollaret's meningitis is a rare self-limiting recurrent aseptic meningitis, which clinically presents similarly to recurrent herpes simplex encephalitis. Classically, it is characterized by the presence of Mollaret's cells on CSF staining. Generally, this diagnosis is reserved for noninfectious cases. Furthermore, there are variable imaging characteristics, often appearing normal on CT/MRI [36-38].

TEACHING POINT

Late relapse of herpes simplex encephalitis is a rare phenomenon, presenting with imaging findings of new enhancing and T2/FLAIR hyperintense herpetic lesions superimposed on atrophic sequala of prior infection. It is the only cause of viral encephalitis with an effective antiviral treatment, and as such should remain on the differential diagnosis for prompt recognition and timely management.

QUESTIONS

Question 1: What is the MOST common presenting symptom for recurrent HSV encephalitis?

1. Fever (applies)
2. Seizures
3. Headache
4. Aphasia
5. Lethargy

Explanation:

1. Fever is the most common presenting symptom. [Fever was the most common presenting symptom (21/27) followed by seizures (12/27)].
2. Seizures is a common presenting symptom, but fever is more common. [Fever was the most common presenting symptom (21/27) followed by seizures (12/27)].
3. Headache is one of the reported symptoms, but is not the most common. [Other reported symptoms include headache, aphasia, consciousness disturbance, drowsiness, and lethargy].
4. Aphasia is one of the reported symptoms, but it is not the most common. [Other reported symptoms include headache, aphasia, consciousness disturbance, drowsiness, and lethargy].
5. Lethargy is one of the reported symptoms, but it is not the most common. [Other reported symptoms include headache, aphasia, consciousness disturbance, drowsiness, and lethargy].

Question 2: What is the MOST common treatment duration of acyclovir for recurrent HSV encephalitis?

1. 7 days
2. 14 days
3. 21 days (applies)
4. 3 weeks
5. 6 weeks

Explanation:

1. 21 days is the most commonly reported treatment duration for recurrent HSV encephalitis. [Most studies reported a 21-day regimen of acyclovir though some clinicians employ longer treatment times…]
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Question 3: What is the ONLY imaging finding specific to

relapse of HSV encephalitis?

1. New herpetic lesions superimposed on old herpetic lesions (applies)
2. T2/FLAIR hyperintensities throughout the cerebral cortex.
3. T2/FLAIR hyperintensities throughout the deep gray matter structures.
4. Gyriform, nodular, and leptomeningeal patterns of enhancement.
5. Extensive white matter edema.

Explanation:

1. New herpetic lesions superimposed on old herpetic lesions is the only specific imaging finding to recurrent HSV. Otherwise, imaging findings overlap with new HSV encephalitis. [The only imaging finding specific to relapse are new herpetic lesions superimposed on old lesions.]
2. T2/FLAIR hyperintensities through the cerebral cortex is not a unique imaging finding of recurrent HSV encephalitis. [Most cases show multifocal T2/FLAIR hyperintensities through the cerebral cortex and deep gray matter structures.]
3. T2/FLAIR hyperintensities through the deep gray matter structures is not a unique imaging finding of recurrent HSV encephalitis. [Most cases show multifocal T2/FLAIR hyperintensities through the cerebral cortex and deep gray matter structures.]
4. Gyriform, nodular, and leptomeningeal patterns of enhancement is not a unique imaging finding of recurrent HSV encephalitis. [Additionally, there are gyriform, nodular, and leptomeningeal patterns of enhancement.]
5. Extensive white matter edema is not a unique imaging finding of recurrent HSV encephalitis. [Some studies report extensive white matter edema, which is unusual.]

Question 4: Which of the following is the MOST commonly reported identifiable trigger for reactivation of latent herpes simplex virus?

1. Pharmacologic-induced immunosuppression
2. Neurosurgical manipulation of previously infected brain parenchyma (applies)
3. Postinfectious autoimmune disease
4. Genetic predisposition
5. Nutritional deficiency

Explanation:

1. Pharmacologic-induced immunosuppression is one of the reported contributing factors to reactivation of latent virus, but surgical manipulation is the most commonly reported trigger. [Pharmacologic-induced immunosuppression has also been found to be a contributing factor in one case of corticotropin treatment of infantile spasms and another case of carbamazepine induced hypogammaglobulinemia.]
2. Neurosurgical manipulation of previously infected brain parenchyma is the most commonly reported trigger. [The most common identifiable trigger for reactivation has been attributed to surgical manipulation of infected brain parenchyma comprising 12 of the cases.]
3. Postinfectious autoimmune disease is one of the reported contributing factors to reactivation of latent virus, but surgical manipulation is the most commonly reported trigger. [Other proposed mechanisms of relapse include postinfectious autoimmune disease and even a genetic predisposition.]
4. Genetic predisposition is one of the reported contributing factors to reactivation of latent virus, but surgical manipulation is the most commonly reported trigger. [Other proposed mechanisms of relapse include postinfectious autoimmune disease and even a genetic predisposition.]
5. Nutritional deficiency is not a reported trigger for reactivation of HSV.

Question 5: Prior the current case, what was the previously longest-reported latency period prior to relapse of herpes simplex encephalitis in a pediatric patient?

1. 21 days
2. 3 months
3. 8.5 years (applies)
4. 13 years
5. 20 years

Explanation:

1. 21 days is the typical treatment duration with acyclovir for recurrent HSV encephalitis 3 months is the minimum latency period to qualify for recurrent HSV encephalitis diagnosis. [Late relapse, defined as recurrent active infection longer than 3 months from the end of antiviral treatment…]
2. 3 months is the minimum latency period to qualify for late relapse of herpes simplex encephalitis. [The data on late relapse of herpes simplex encephalitis, defined as longer than 3 months after antiviral treatment, is limited with only 27 documented cases.]
3. Prior to the current case, 8.5 years was the longest reported latency period prior to late recurrent HSV encephalitis. [This case is unique in that it represents the longest documented idiopathic relapse (over 13 years) of herpes simplex encephalitis in a pediatric patient with the second longest being 8.5 years.]
4. The currently reported case had a latency period of 13 years, which is the new longest documented time prior to relapse. [This case is unique in that it represents the longest documented idiopathic relapse (over 13 years)]
5. 20 years is a longer latency period than in any reported idiopathic cases of late recurrent HSV encephalitis. [This case is unique in that it represents the longest documented idiopathic relapse (over 13 years)].

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FIGURES

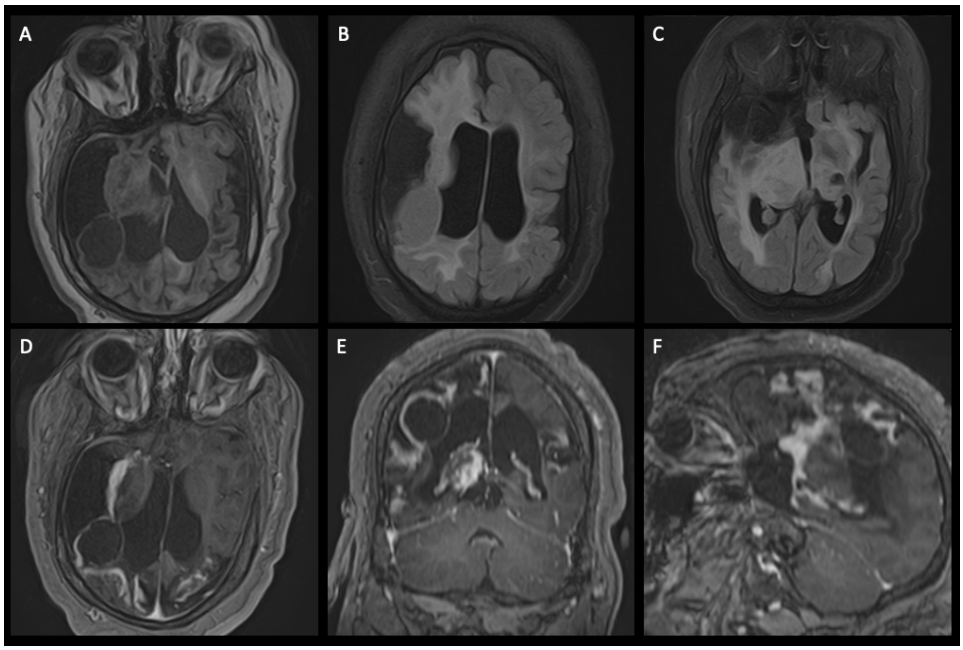

Figure 1: 14 year old female with recurrent HSV encephalitis.

Findings: MRI Brain T1 axial sequence (1A) reveals a cystic lesion within the right parietal lobe measuring 2.3 x 3.0 x 2.3 cm. Multifocal cystic encephalomalacia of the right greater than left cerebral hemispheres is also present. T2/FLAIR axial sequence (1B + 1C) reveals edema throughout the bilateral cerebral hemispheres and right greater than left thalami and basal ganglia. T1 post-contrast axial (1D), coronal (1E), and sagittal (1F) sequences show peripheral enhancement of the lesion and gyriform and leptomeningeal enhancement of the right frontal, parietal, and temporal lobes.

Technique: Phillips Ingenia Ambition X 1.5 Tesla MRI T1 pre and post contrast sequences with 5mmol Gadavist, T2/FLAIR sequence

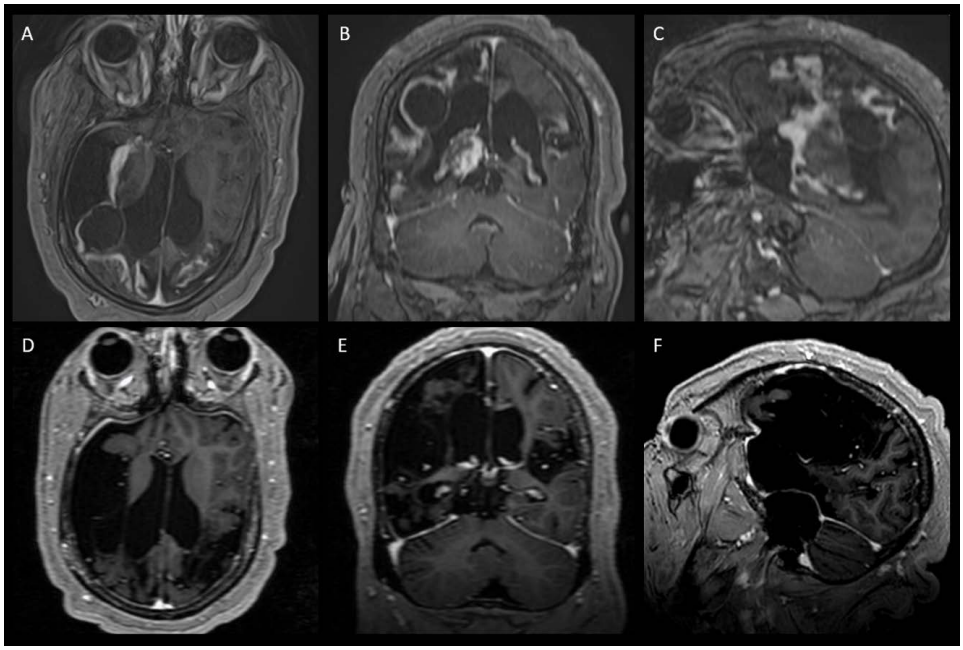

Figure 2: 14 year old female with recurrent HSV encephalitis.

Findings: Comparison of acute presentation MRI brain T1 post-contrast axial (**2A**), coronal (**2B**), and sagittal (**2C**) sequences with prior MRI brain T1 post-contrast axial (**2D**), coronal (**2E**), and sagittal (**2F**) sequences from 1.5 years earlier show that the right parietal cystic lesion, peripheral enhancement, and leptomeningeal enhancement are new from prior.

Technique: Phillips Ingenia Ambition X 1.5 Tesla MRI T1 pre and post contrast sequences with 5mmol Gadavist

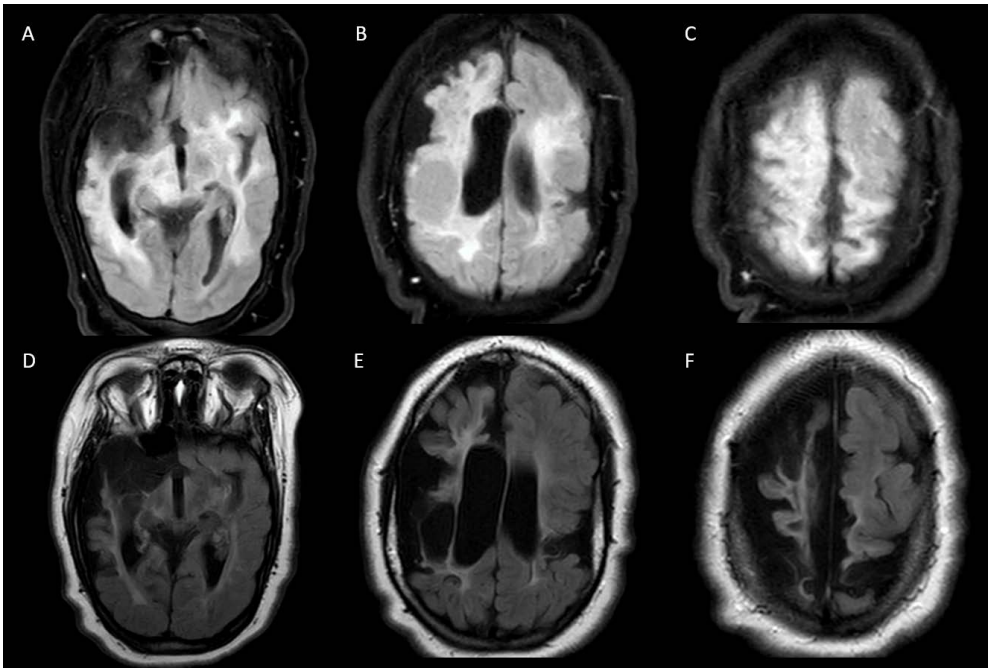

Figure 3: 14 year old female with recurrent HSV encephalitis.

Findings: Comparison of acute presentation MRI brain T2/FLAIR axial sequences (**2A + 2B + 2C**) with prior MRI brain T2/FLAIR axial sequences from 1.5 years earlier (**2D + 2E + 2F**) show that the edema throughout the bilateral cerebral hemispheres is new from prior.

Technique: Phillips Ingenia Ambition X 1.5 Tesla MRI T2/FLAIR sequence

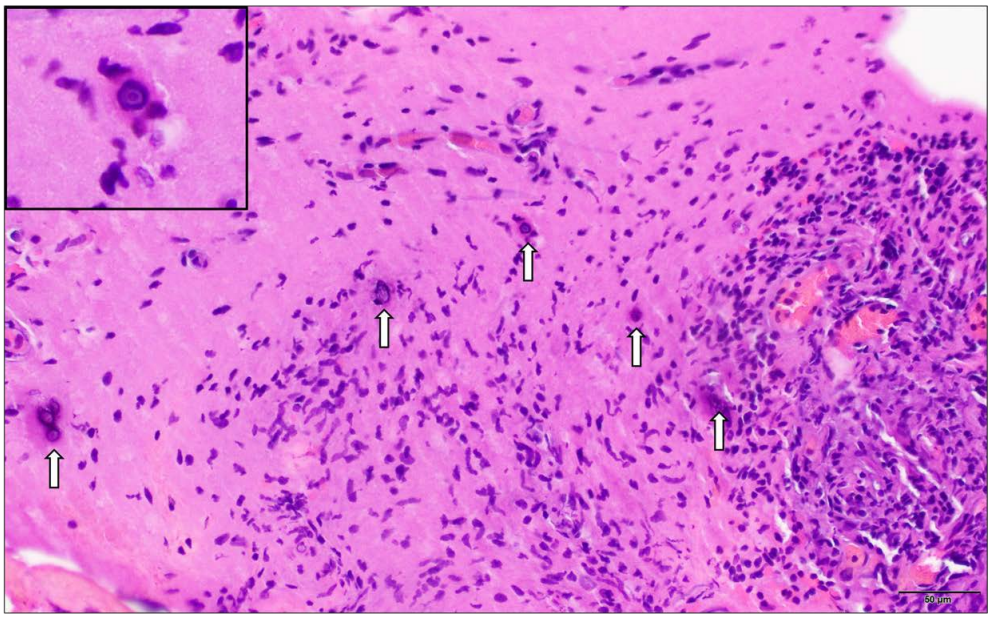

Figure 4: 14 year old female with recurrent HSV encephalitis.

Findings: Biopsy sections stained with hematoxylin and eosin show brain tissue with chronic lymphocytic inflammation and scattered abnormal cells with Cowdry type A nuclear inclusions (arrows), which are characterized by nuclei with an irregular rim of condensed chromatin with central eosinophilic material separated from the marginated chromatin by a clear zone (inset). Magnification: 200x (inset: 400x)

Summary table:

Etiology	The leading hypotheses are latent reactivation, post-infectious autoimmune disease, and genetic predisposition.
Incidence	5-26% incidence of relapse in general, and there are only 27 documented cases of specifically late relapse.
Gender Ratio	Greater prevalence among females.
Age Predilection	Greater prevalence among pediatric patients.
Risk factors	Surgical manipulation of infected herpetic brain lesions was by far the most common identifiable trigger.
Treatment	Treatment of relapse is the same as primary infection which is intravenous acyclovir (most commonly a 21-day regimen) with some studies reporting the addition of corticosteroids.
Prognosis	Timely initiation of acyclovir treatment was associated with the best outcomes. The most common was persistent mild neurologic deterioration from baseline.
Findings on imaging	New enhancing and T2/FLAIR hyperintense herpetic lesions superimposed on atrophic sequalae of prior infection. Otherwise, indistinguishable from primary infection.

Differential table:

Recurrent HSV Encephalitis	CT: hypodensity of affected regions, though CT is often negative. MRI: overlapping findings as primary HSV encephalitis described below, though recurrent HSV encephalitis will demonstrate these findings superimposed on old herpetic lesions.
Primary HSV Encephalitis	CT: hypodensity of affected regions, though CT is often negative. MRI: symmetric or asymmetric T2/FLAIR hyperintensity most-commonly of the temporal lobes, then parietal lobes, but may involve any lobes' cortical or white matter, typically sparing the basal ganglia. Variable patterns of enhancement including gyral and leptomeningeal enhancement.
Autoimmune limbic encephalitis	MRI: asymmetric cortical T2/FLAIR hyperintensity of the mesial temporal lobes and limbic systems. Lateral temporal lobe and insular lobes are less commonly involved. The basal ganglia are frequently involved.
Diffuse Low-Grade Astrocytoma	CT: iso/hypodense regions of parenchymal expansion and mass effect. MRI: Region of T2 hyperintensity primarily involving the supratentorial white matter, suppressed T2 signal on FLAIR sequence, and expansion of affected brain parenchyma.
Acute Stroke	CT: hypoattenuation in a vascular distribution. CTA: can identify vascular etiology such as an embolus or stenosis. MRI: T2/hyperintensity and restricted diffusion in a vascular distribution.
Mollaret's Meningitis	Variable with no definitive imaging characteristics. CT/MRI can often appear normal.

KEYWORDS

Recurrent herpes simplex encephalitis; relapsed herpes simplex encephalitis; encephalitis; herpes encephalitis; pediatric