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Case Report

Recrudescence, A Common, But Minimally Cited Neurological Phenomenon, with Review of the Literature

Mackenzie L Montero[1], Korrina Siddiqui[1], Burton Tabaac[1,2]*

[1]University of Nevada, Reno School of Medicine, Reno, NV, USA

[2]Carson Tahoe Health, Department of Neurology, Carson City, NV, USA

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***Corresponding author:** Dr. Burton Tabaac, MD, University of Nevada, Reno School of Medicine, Reno, NV, USA, E-mail: burton.tabaac@gmail.com

A B S T R A C T

Stroke recrudescence, the reappearance of previously resolved stroke-like symptoms without detectable acute lesions on MRI following an acute stressor, remains a lesser reported phenomenon in the vascular neurology literature. The sparse documentation capture of this topic and lack of unified terminology makes this a frequently undiagnosed phenomenon in the neurology specialty. This paper reviews clinical attributes, common triggers, alternative diagnoses, and potential interventions to aid in the diagnosis of stroke recrudescence, and to aid in prevention of inappropriate diagnoses attribution. Triggers encompass a spectrum inclusive of infections to psychosocial stressors, with CNS depressants like benzodiazepines and opioids emerging as significant common contributors. Refining traditional stroke workup methods is crucial to distinguish recrudescence from acute strokes. By presenting existing literature and providing clinical expertise, this paper aims to increase awareness among healthcare providers, ultimately enhancing diagnostic accuracy and the quality of care for individuals experiencing this recurrent and common neurological phenomenon.

Keywords: Stroke recrudescence; Acute lesion; Vascular neurology

1. Introduction

Recrudescence has been characterized variously as a "differential awakening" (Cucchiara), a "reexpression of an old stroke" (Selmin), and a "reemergence" (Lazar) in the literature, contributing to a lack of consistency in the medical terminology employed to describe this not uncommon occurrence[1-3]. Given the significance of this issue, it is imperative to review the current literature to establish a comprehensive framework for this entity, with the ultimate goal of curtailing unnecessary medical investigations and enhancing diagnostic precision.

Stroke recrudescence, characterized by the reappearance of previously resolved focal stroke deficits following an acute stressor, without detectable acute lesions on MRI, remains a relatively unexplored phenomenon within the vascular neurology subspecialty[4,5]. Frequently mistaken for acute strokes, stroke recrudescence often leads to unnecessary and costly imaging and changes in medication recommendations. Existing literature suggests that recrudescence affects approximately 1 in 10 patients displaying symptoms of a second stroke like event, underscoring the need for in-depth education that elucidates this presentation. This education pursuit can elevate awareness regarding this commonly encountered occurrence and subsequently minimize length of stay, conserve cost, and enhance patient care[5].

Our objective is to delve into the clinical attributes, common triggers, and potential interventions related to stroke recrudescence. By offering clinical insights and a comprehensive review of the cited literature, we seek to empower clinicians in accurately diagnosing, and effectively managing, instances of stroke recrudescence.

2. Case Presentation

A 78 year-old woman presents to the emergency room with 12 hours of worsening right-sided acute on chronic weakness and worsening speech deficits described as word find difficulty, and associated urinary frequency and dysuria. Medical history includes history of left MCA ischemic infarct presenting with right side facial droop and right side arm weakness, treated with tPA, paroxysmal atrial fibrillation untreated, hypertension treated with lisinopril and controlled type 2 diabetes managed with sliding scale insulin.

Physical exam findings showed a lethargic and AxOx3 woman with noticeable focal neurological deficits. Neurological examination showed a right sided facial droop, mild dysarthria, 3/5 strength, with decreased sensation in right upper extremity to pin compared to 5/5 strength and intact sensation of the left upper extremity. Noncontrast CT revealed a chronic infarct territory localized to the left frontal and temporal lobes, but with no evidence of acute ischemia or hemorrhage. Urine analysis showed positive nitrates and positive leukocyte esterase, with urine culture growing gram negative rods suggestive of E.coli. The patient's neurological deficits dramatically improved after treatment of the urinary tract infection via antibiotic regimen of trimethoprim-sulfamethoxazole.

3. Discussion

3.1 Identifying triggers and provoking factors

Recrudescence manifests with symptoms that closely resemble that of the patient's initial stroke symptomatology, albeit typically with less severity. This characteristic sets it apart from novel strokes, which infrequently impact the identical previously affected brain region. Consequently, this underscores the significance of conducting a meticulous review of patients' medical recordsto accurately discern instances of recrudescence.

A plethora of potential triggers can precipitate recrudescence, illustrated in (**Table 1**). An enlightening study by Jun-O-Connell et al. revealed that infections (26.5%), metabolic factors (20.6%), hemodynamic fluctuations (5.9%), psychosocial stressors or other triggers (8.8%), as well as the presence of multiple stressors (38.2%) were the most prevalent categories precipitating recrudescence[5]. In line with these findings, a retrospective analysis identified hypotension, hyponatremia, fever, insomnia, and stress as factors correlated with the onset of recrudescence[6].

The diverse array of triggers contributing to recrudescence accentuates the necessity for a standardized diagnostic approach aimed at evaluating both the occurrence of recrudescence and its underlying triggers. Such an approach might encompass a comprehensive patient history, toxic metabolic panels, complete blood counts, and monitoring of vital signs.

3.2 Provoking factors

Specific retrospective and prospective studies highlighting provoking factors for recrudescence include but are not limited to the following:

3.3 CNS Depressants and Recrudescence

Numerous significant factors have been identified as potential triggers for recrudescence, among them of which includes the use of central nervous system (CNS) depressants. Multiple research studies have established a connection between recrudescence and the consumption of controlled substances. The first notable observation of this relationship dates back to 2002, when an article reported the reappearance of stroke symptoms in a patient subsequent to the administration of benzodiazepines[3]. Since this citation, subsequent investigations have documented CNS depressants inclusive of anesthetic agents, benzodiazepines, and opioids as culprits for inciting recrudescence[4,6].

Table 1: Precipitating factors that can lead to recrudescence presentation.

Provoking factors	Examples
Infectious	UTI, viral, bacterial
Metabolic dysfunction	Hyper/hypoglycemia, hyponatremia
Autonomic	Hyper/hypotension
Physiological stress	Medication use - opiates, benzodiazepines, antiepileptics
Psychosocial stress	Stress, insomnia

A limited number of retrospective studies have indicated a correlation between opioid use following an initial stroke incident and the likelihood of recrudescence. For instance, a case report featured a 44-year-old right-handed woman who, after experiencing a right hemispheric stroke, suffered from a week of intense unyielding pain rated in severity as a 9/10. Her diagnosis encompassed vaso-occlusive pain crisis due to a history of sickle cell anemia leading to the administration of a CNS depressant. Remarkably, within a few hours she exhibited acute severe focal neurological deficits that mirrored the presentation of her prior known stroke, occurring three years prior. In this case, the trigger for symptomatology and clinical worsening was attributed to intravenous hydromorphone administration[7]. Another case report narrated the story of a 67-year-old man initially presenting with subarachnoid hemorrhage and subsequently experiencing symptoms akin to a lacunar stroke after undergoing a CT angiogram. Even thoughthe patient and family denied any previous stroke-related symptoms, dedicated neuroimaging revealed evidence of a pre-existing chronic lacunar infarct. In this context, the administration of benzodiazepines and opioids during the CT angiogram was considered a likely trigger for recrudescence[6].

Some prospective studies have undertaken the exploration of the CNS depressant theory as a trigger for recrudescence by conducting midazolam challenges. In one study, a total of 8 patients, 5 with left-sided symptoms and 3 with right-sided symptoms, who had experienced strokes ranging from 7 days to 6 years prior, displayed similar symptoms to their initial strokes when subjected to midazolam challenge. Intravenous midazolam was administered until mild drowsiness was observed. Patients were evaluated during the period of sedation and again after a 2-hour interval when the sedative effects had worn off. The results indicated that among the patients with left hemispheric strokes, 5 demonstrated a recurrence or exacerbation of their initial right hemiparesis and aphasia, but no signs of left neglect. Conversely, the 3 patients with right cerebral strokes displayed the reappearance of left hemiparesis and left visual field neglect, with no aphasia. Importantly, all patients returned to their baseline conditions after a two hour interval clinical assessment[3].

Differentiation between Post-Stroke Recrudescence vs. Stroke vs. OtherStroke-Mimicking Etiologies

The necessity for a coherent and uniform definition and set of criteria for recrudescence is underscored by the need to categorize cases that might potentially align with this definition

but cannot be definitively categorized as such. In an already broad list of differentials for neurological deficits, recrudescence is set apart, yet similar to other common emergent insultssuch as stroke or seizures (**Table 2**). Instances of this ambiguity have been identified within retrospective cases. For instance, one case presented with stroke-mimicking symptoms: A 70-year-old woman exhibited right-eye abduction deficit, facial muscle control issues, and difficulty closing the eyes two weeks subsequent to the onset of painful red fluid-filled rashes. Initially diagnosed with shingles and diabetic cranial neuropathy, four years later she displayed left-sided facial paralysis, an inability to raise her left eyebrow, weakened left eye blink, and an ataxic gait alongside vesicular eruptions and crusting erupting on the left side of her neck.

These manifestations were consistent with Ramsay Hunt syndrome involving the C2 and C3 dermatomes. A subsequent incident revealed no acute infarction on imaging but with chronic pontine infarction and periventricular ischemic changes, which may have accounted for the clinical findings four years prior[8]. This case exemplifies a combination of components suggestive of recrudescence while also featuring elements that diverge from the phenomenon. In another case, a 59-year-old woman exhibited mild COVID-19 symptoms with non-specific neurological complaints such as loss of olfaction, diminished taste sensation, and fatigue, but began having a degree of memory impairment without a neurological exam captured. Two months later she presented with worsening cognitive impairment as well as sensory deficits andnovel right sided weakness. Chronic ischemic stroke in the setting of recent COVID-19 infectionmanifesting as memory impairment and acute neurological deficits two months later may be related to stroke recrudescence during the recovery phase of the infection. Due to the ambiguity presented in the cases aforementioned, this underscores the imperative for widespread awareness within the medical community regarding the spectrum of the recrudescence phenomenon and its varied presentations. This will foster a comprehensive understanding and proper protocols, such as conducting and reviewing comprehensive neurological histories and performing complete neurological examinations.

3.4 Evaluating Traditional Medication and Imaging

For individuals not well-versed in the concept of recrudescence, these occurrences might bear resemblance to novel acute strokes, even in cases where preventive stroke medications are being taken with compliance. Unfortunately, this resemblance can unwittingly prompt the initiation of unwarranted supplementary antiplatelet or anticoagulant treatment, aligning with prevailing AHA/ASA stroke guidelines. While intended to mitigate risk, this response may inadvertently heighten the potential for bleeding and other adverse outcomes in a patient without added benefit[9]. A systematic review underscored that six patients presented (4%), who were ultimately diagnosed with recrudescence, were subjected to unnecessary administration of tissue plasminogen activator (tPA), a relevant potential consequence of misdiagnosis and pursuing inappropriate treatment pathways[10].

Noting improvement of stroke-like symptoms with removal of triggers, it is important to considerhow improving the traditional workup of stroke would be beneficial for both patients and providers. One thing to consider as it pertains to completing a stroke workup is the indication for obtaining vessel imaging such as a CTA series. In the cited literature, imaging studies conducted on patients with post stroke recrudescence, in majority of cases, revealed no new acute infarct or hemorrhages, whereas a new stroke with new neurological deficits would show infarct or hemorrhage in a different area of the brain[10]. Although a CT and/or CTA study series is relatively quick and easy to obtain in emergent situations, this leads to an extended window for the patient's potential improvement. This may also result in an augmentation of hospital expenses and over-allocation of resources. It is vital to have someone on the emergency team reviewing history of prior stroke(s) and comparing these findings to the presenting signs and symptoms of the current episode declared. If novel signs and symptoms are apparent, then continuing with the standardized stroke protocol is appropriate. If the same symptomatology is discerned, then recrudescence ought to be considered with workup focusedon potential provoking factors; this can expeditiously narrow the differential of potential etiologies, and targeted treatment be applied more promptly.

Table 2: Differential diagnosis and characteristics for recrudescence and recrudescence mimics.

Differential	Onset	Signs andsymptoms	Clinical course	Imaging
Recrudescence	Gradually abrupt	New insults that are similar if not the same to previous stroke, mild to moderate	Removing provoking trigger provides progressive recovery with some fluctuationof deficits	No evidence of new stroke, occlusion or increase in stenosis,only chronic infarct or hemorrhagic area
TIA, Ischemic or Hemorrhagic Stroke	Abrupt	New insults thatare dissimilar to previous stroke,mild to severe	Thrombolysis, percutaneous intervention provides prompt resolution	Rarely can show new infarct or hemorrhage with dilated vessels from reperfusion, new occlusion, or increase in stenosis, along with chronic infarct or hemorrhagic area
Seizure-related deficits	Abrupt with seizure disorder	New insults that are worse than previous stroke symptoms, associated with post-ictal confusion, tongue biting, incontinence, mild to severe	Baseline resolution of insults gradually	No evidence of new stroke, occlusion or increase in stenosis,but can show abnormal DWI

4. Conclusion

In conclusion, the phenomenon of recrudescence, characterized by the reemergence of previously resolved stroke-like symptoms following acute stressors, presents a challenging and relatively unexplored area within the realm of vascular neurology. It is

important to be aware ofthe various aspects of this phenomenon, shedding light on its clinical attributes, common triggers, and potential interventions. The comprehensive review of literature underscores the importance of a standardized diagnostic approach, emphasizing the need to differentiate recrudescence from other stroke-related conditions and stroke-mimicking etiologies.

Triggers for recrudescence encompass a wide spectrum of factors, ranging from infections and metabolic dysfunction to autonomic disturbances and psychosocial stressors. Notably, CNS depressants, such as benzodiazepines and opioids, have emerged as significant contributors to the occurrence of recrudescence, prompting the need for heightened vigilance when administering such medications to stroke survivors.

Misdiagnosis of recrudescence as a new stroke can lead to inappropriate treatment interventions, emphasizing the necessity for accurate differential diagnosis. This paper highlights the potential benefits of refining traditional stroke workup methods, including the judicious use of imaging, such as CT angiography, to discern between recrudescence and acute strokes.

By aggregating and summarizing existing research, this paper contributes to a better understanding of recrudescence and its diverse manifestations. Awareness among healthcare providers of this phenomenon's intricacies and triggers can lead to improved patient care, timely interventions, and informed treatment decisions. Ultimately, a deeper comprehension of recrudescence can enhance diagnostic accuracy, streamline medical investigations, and elevate the quality of care provided to individuals experiencing this recurrent neurological occurrence.

5. Data Availability

All data reviewed and discussed was found in scientific papers which were cited in the references section.

6. Conflict of Interest

All authors affirm there are no conflicts of interest with research endeavors.

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