



Syndromic Approach: The Febrile Stroke

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Abstract: Infectious disease practitioners are often tasked with evaluating fever in the setting of acute stroke. Although fever is often considered a host response to acute ischemia, underlying infections are identified in approximately one-fourth of cases. Physicians should be vigilant in evaluating for infectious triggers of stroke, as well as potential infectious consequences of ischemia and direct infectious invasion of the central nervous system leading to stroke.

Keywords: Stroke; ischemia; aspiration pneumonia; endocarditis; HIV; COVID-19; neurosyphilis; tuberculosis; meningitis; cryptococcus

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Introduction

Every year, approximately 800,000 patients are admitted in the United States after presenting with a transient ischemic attack or acute cerebral infarction [1]. Fever is a relatively common presenting sign of acute stroke, seen in up to 50% of cases [2]. Most often, fever is a direct consequence of the stroke itself, correlating with initial stroke severity and lesion size [2]. In approximately 25% of the cases, however, fever can be a result of an occult infection, either as a potential trigger (i.e., urinary tract infections) of a stroke, or as consequence of (e.g., aspiration pneumonia) [3]. More rarely, certain infections can have direct invasion of the central nervous system and act as the main causative agent of the ischemia itself [4].

Here, we present a case of stroke associated with fever that a private infectious disease practitioner may be asked to consult on, with a review of the most common differential diagnoses that should be entertained.

Clinical Vignette

A 42-year-old male with a history of hypertension, HIV/AIDS (with a known CD4 count of 68), and intravenous drug abuse (IVDA) presents to the hospital with a 6 h history of sudden aphasia and left

upper extremity weakness. Upon presentation to the ER, he noted to be tachycardic and tachypneic with a temperature of 38.9 °C. Examination confirms the aphasia and left upper extremity weakness. Notable findings also include a soft holosystolic murmur with clear lungs. No rash is seen. Chest imaging is negative for any acute findings and urinalysis reveals 1–5 WBC with trace nitrites. Blood cultures have been sent. Head CT demonstrates a diffusion defect within the right middle cerebral artery. Acute right MCA stroke is confirmed by subsequent MRI/A.

Infectious disease consultation has requested an evaluation of fever in the setting of acute stroke in this patient.

Differential Diagnosis

After the initial assessment of a patient, a differential diagnosis list can then be generated using clues obtained from relevant past medical history, pertinent physical findings, and laboratory or radiographic data. Potential etiologies of fever in our stroke patient should include the following:

- **Host response to ischemia**
 - Increased body temperature represents an adaptive host response and is usually seen within the first 24 h of presentation of an acute ischemic event. Fever typically correlates with infarct volume and is associated with a poorer neurologic outcome in stroke patients [5]. Although no infectious processes are identified within this subset, one should continue to evaluate for alternative causes of fever to avoid further morbidity and mortality, however.
- **Infectious triggers**
 - Systemic infections can potentiate an inflammatory response with the release of cytokines and subsequently encourage clot formation, thereby increasing the risk of ischemia in patients that may have a predisposition to stroke (i.e., arteriosclerosis, diabetes, hypertension, hyperlipidemia) [4]. The most common infectious trigger that has been identified in patients is a urinary tract infection. The risk of stroke within 30 days of a UTI is three times the usual risk when all factors remain equal [6]. A screening urinalysis is recommended in stroke patients presenting with fever.
- **Consequences related to neurologic complications of acute stroke**
 - Stroke patients with an impaired swallowing mechanism are at increased risk for aspiration pneumonia, a common cause of fever in hospitalized patients. Up to 1/3 of stroke patients suffer from pneumonia during their hospitalization for an acute CVA [7]. If initial chest imaging demonstrates no acute findings, it is imperative to repeat the study during the hospital course, especially if a patient remains febrile.
- **Embolic phenomenon related to infection**
 - Embolic phenomenon related to infectious endocarditis is a rare cause of ischemic stroke, accounting for less than 10% [8]. However, it is associated with a high morbidity and mortality; thus, diagnosis is paramount. Blood cultures and echocardiograms should be performed routinely in febrile stroke patients. Endocarditis with embolic features can also be related to non-infectious causes, including non-bacterial thrombotic endocarditis, which is most commonly associated with malignancy, and Libman–Sacks endocarditis, seen in SLE and the antiphospholipid syndrome. These forms of endocarditis may not present with fever, however [8].
- **Infections causing direct invasion of the central nervous system**

- Several infectious pathogens have been implicated as causative agents of ischemia by way of direct CNS invasion. Unless a patient has a significant degree of immunosuppression, fever is typically seen with direct CNS invasion. Mechanisms of ischemia may include vasculitis and vasospasm related to basilar meningitis or the formation of hypercoagulable states in relation to endothelial dysfunction due to localized infection [4]. More often than not, clinical or epidemiological clues may offer insight as to the likelihood of involvement of these infectious processes and evaluation should be tailored accordingly.
- Bacterial infections
 - Neurosyphilis classically causes an obliterative endarteritis of medium- and large-sized blood vessels 5–12 years after initial infection. It should be considered in any young adult with no traditional risk factors for ischemia, particularly if strokes are recurrent and affect the MCA territory [4].
 - Tuberculosis meningitis can cause stroke in up to 15–60% of patients [9]. Ischemia occurs as a result of tubercle rupture, subsequently causing a massive inflammatory response, leading to intimal proliferation in arteries and veins, most commonly at the base of the brain [10].
- Viral infections
 - HIV infection has been implicated in cerebral ischemia by way of direct CNS artery invasion/vasculopathy or indirectly related to opportunistic infections, cardioembolic phenomenon, drug use, or metabolic syndrome. Since CNS invasion can occur during acute retroviral syndrome, HIV testing may be warranted in patients with appropriate clinical risk factors. Fever may not necessarily be seen in these patients [4].
 - Acute CVA has been seen in approximately 5% of patients hospitalized with SARS-CoV-2 infection [11], occurring by activation of the coagulation and inflammatory pathways. Acute CVAs in this cohort are typically seen in those with pre-existing conditions for increased risk of stroke, although case studies have demonstrated the occurrence of large-vessel strokes in younger patients with COVID-19 with no underlying risk factors [11]. Given the high background prevalence of COVID-19 infection worldwide at the present time, screening should be performed on all stroke patients presenting to the hospital, especially those with fever.
- Fungal infections
 - Meningitis related to Cryptococcus spp. is usually noted in immunocompromised patients (50% in HIV), and can be complicated by stroke in up to 26% of cases [12]. These strokes, which are commonly multiple and lacunar, also affect the basal ganglia [4].

Discussion

Infectious disease practitioners are commonly asked to evaluate fever in the face of acute stroke. Given the clinical clues noted in our patient, the evaluation for etiology of fever could be extensive, but in general, could also be extrapolated to the general stroke population at large. Initial potential diagnoses should include infectious triggers, as well as infectious processes related to neurological compromise itself and embolic phenomenon. Admission work-up for all patients presenting with acute stroke should include screening urinalysis (and urine culture if indicated), blood cultures, echocardiogram, and chest radiography. If risk factors or presenting complaints suggest a diagnosis

of either COVID-19 or syphilis, COVID-19 testing and screening RPR should be performed. The additional evaluation for direct infectious CNS involvement could also be included in patients depending on underlying medical or epidemiological history. With regards to our case patient with known AIDS, one could consider proceeding with lumbar puncture for the evaluation of neurosyphilis, tuberculous, or cryptococcal meningitis in the face of progressive neurological deficits with no etiology of ongoing ischemia identified.

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