Case Studies

Successful Use of Intravenous Tissue Plasminogen Activator as Treatment for a Patient with Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy: A Case Report and Review of Literature

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Background: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is considered a common cause of hereditary stroke caused by mutation of the *NOTCH3* gene. Evidence against the use of intravenous tissue plasminogen activator (IV tPA) has been suggested due to possibility of hemorrhage. We present a case of a patient with CADASIL who was successfully treated using IV tPA. *Methods:* A case description of a female patient who presented with stroke-like symptoms was a previously known case of CADASIL. Review of literature was done using search terms such as CADASIL, NOTCH3, and intracranial hemorrhage or brain hemorrhage. *Results:* A 35-year-old female patient presented to the emergency department with acute onset hemiparesis, hemiparesthesia, and motor aphasia with a National Institutes of Health Stroke Scale score of 8. The patient was a previously diagnosed case of CADASIL with a positive NOTCH3 mutation. Computed tomography scan showed no large vessel occlusion with no perfusion deficient. Patient was within window for IV tPA treatment which was administered, and she subsequently had marked improvement of all symptoms. *Conclusion:* There is slight evidence against the use of IV tPA for CADASIL patients who present with stroke-like symptoms but nothing is concrete. It has also been suggested that some patients who are undiagnosed have been treated with IV tPA with favorable results but unfortunately are not reported. Further studies and or large clinical trials could be beneficial for those patients who may benefit from IV tPA and who have previously been diagnosed with CADASIL.
Key Words: Stroke—CADASIL—tPA—genetic—complications.

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Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a monogenetic cause of stroke secondary to mutations of the *NOTCH3* gene on chromosome 19. CADASIL is characterized by a constellation of migraine with aura and subcortical strokes that lead to cognitive dysfunction.[1] The pathophysiology of CADASIL is not well understood, but at least 3 theories have been proposed.[2] On the basis of histopathology, the disease is characterized

by degeneration of the medial smooth muscle cells and replacement with nonamyloid eosinophilic granular material.[3] Large vessel occlusion or cortical stroke in CADASIL is rare and the P380P mutation may be protective, but the incidence is not zero.[4,5] A PubMed search using the terms "CADASIL" and "thrombolysis" yields only 1 result, which lists thrombolysis as a contraindication for CADASIL patients because of presumed hemorrhage risk.[6] Intracranial hemorrhages (ICH) have been described as spontaneous events in CADASIL patients, and microbleeds being described in an estimated 31%-69% of CADASIL patients.[7-9]

In this paper, we present a case of a known CADASIL patient presenting as an acute stroke to our emergency department and successfully being treated with intravenous tissue plasminogen activator (IV tPA) without ill effects, which will represent the first published case of IV tPA usage in a known CADASIL patient. We also present a brief literature review of the risks of hemorrhagic complications in CADASIL.

Case Report

A 35-year-old female presented to our emergency department with acute onset of right-sided hemiparesis, hemiparesthesia, and transcortical motor aphasia, resulting in a National Institutes of Health Stroke Scale (NIHSS) score of 8.[8] The patient had a known diagnosis of CADASIL with positive NOTCH3 mutation, specifically at C406T (Arg110Cys), and prior history of subcortical strokes. She took aspirin 325 mg and atorvastatin 40 mg daily prior to admission and had been compliant with these medications. She immediately underwent a computed tomography scan with angiography that showed no large vessel occlusion, perfusion deficit, acute loss of gray–white junction, or hemorrhage. She was within the extended window (3-4.5 hours) for IV tPA treatment. After a lengthy discussion of risks and benefits of treatment, including the unclear nature of her hemorrhage risk, the patient opted to try IV thrombolysis with tPA. Within the next several hours after treatment, the patient's symptoms improved and she felt back to her baseline. She underwent a magnetic resonance imaging brain scan which showed no new areas of diffusion restriction and no areas of gradient echo signal positivity, but showed extensive subcortical T2 hyperintensity, which was seen throughout including the anterior temporal regions consistent with prior subcortical infarcts and the diagnosis of CADASIL. The patient was discharged and continued on her current regimen of secondary stroke risk reduction of aspirin and atorvastatin.

Methods of Literature Review

To explore published cases of ICH in CADASIL, PubMed was searched using a combination of terms (CADASIL, OR NOTCH3, OR "Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy") AND ("intracranial hemorrhage" OR "brain hemorrhage" OR "brain bleed") which was more inclusive than prior published literature review method.[10] The abstracts of each identified paper were evaluated for the inclusion criteria. Inclusion criteria were case reports or series that included patients' specific information as to possible risk factors and associations in CADASIL patients. Exclusion criteria were papers that were not peer reviewed, opinion pieces, not in English, and reviews that did not have at least 1 case reported within it. Papers meeting the inclusion criteria were read in complete form. The bibliographies of the identified papers were hand searched for references that were missed by the PubMed searches.

Literature Review Results

The published cases of ICH are summarized in Table 1, which admittedly only represents 9 additional cases after the work of Rinnoci et al.[10] A PubMed using the above criteria yielded 62 papers with the terms used by Rinnoci et al yielding 12 papers.[10]

In total, 35 cases of ICH were identified in the literature, with one being excluded secondary to it not being in English.[24] Of the identified case, the average age was 58 years old. Antiplatelet agents were identified for at least 9 of these cases, representing only 26% of all the cases reported. Microbleeds were identified in nearly all cases of ICH. There were no cases of hemorrhage related to IV thrombolysis usage in CADASIL.

Discussion

CADASIL is typically progressive and debilitating with 85% of patients having strokes starting anywhere from 19 to 67 years old with a global decline in function, mood disorder, and a median age at death of 65 years in men and 71 years in women.[25,26]

CADASIL has also been associated with microbleeds and overt ICH. The incidence of microbleeds has been reported in 31%-69% of CADASIL patients.[8,9] Our search only yielded a total of 34 published cases of nonmicrobleed hemorrhage in patients with CADASIL with microbleeds being present in most of the published cases of ICH (Table 1). The risk of hemorrhage may be increased because of loss of autoregulation, which may lead to microbleeds, and/or the hemorrhagic conversion of prior ischemic strokes,[27] but the actual mechanism is unknown.[9,28] Additional risks for hemorrhage are age,[9] diabetes, and hypertension.[9,29] In one study that showed a correlation of hemorrhage with antiplatelet therapy, once patients were corrected for age this association was no longer statistically significant.[7]