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Acute Ischemic Stroke in Chronic Kidney Disease; Dichotomy of Thrombolytic Therapy

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Abstract

Atheroembolic renal disease (AERD) is underreported in the literature due to need of high index of suspicion. As AERD is characterized by the presence of triad; precipitating event, renal failure and evidence of peripheral cholesterol embolization. Need of tissue biopsy for confirmative diagnosis reduces reporting. We report the dichotomous nature of thrombolytic therapy for an acute ischemic stroke (aIS) in a chronic kidney disease (CKD) patient with extensive atherosclerotic vascular disease. Like a two face of a coin this patient benefitted from thrombolysis resulting in reversal of his Left upper extremity weakness at the cost of AERD with dialysis dependency. But the risk of AERD involved with thrombolytic therapy for acute ischemic stroke in CKD should not detain from using tissue-type plasminogen activator (t PA). The oxidative stress, elevated calcium-phosphate product, hyper homocysteinemia, inflammation, and anemia of CKD may potentiate atheromatous plaques dislodgment. But future endeavors to overcome these paucities are awaited.

Keywords

atheroembolic renal disease (aerd); chronic kidney disease (ckd); thrombolytic therapy

Introduction

Stroke is the fifth leading cause of death in the United States and a major cause of adult disability [1, 2]. Nearly 800 thousand people suffer from stroke each year in US [2].

Chronic kidney disease (CKD) is associated with an increased risk for stroke [3]. The stroke risk is four to tenfold higher among ESRD patients (pt) in comparison to general population[4, 5]. CKD pts carry higher risk of about 1.5-3 times for stroke[6, 7]. CKD itself is not an independent risk factor for stroke, but becomes so when it's associated with co-morbidities anemia, cardiovascular disease or macro albuminuria[3].Most clinical trials have demonstrated the hemorrhagic complication of thrombolytic therapy. But here we present complication of renal cholesterol embolization following tPA therapy in a CKD patient with symptomatic stroke and the dichotomy of the usage of thrombolytic therapy in advanced CKD pts.

Case Presentation

NE 66 year old Caucasian male with history of hypertension, hyperlipidemia, severe atherosclerotic vascular disease with right carotid stenosis of 60-69%, CKD 3, reformed smoker presented to emergency (ER) with complaints of weakness, unable to move his left upper extremity

and loss of hand grip with numbness since 1 30 am. Patient (pt) noticed this when he got up to use restroom and was rushed to local ER for evaluation. On examination pt was noted to have acute ischemic stroke (aIS) involving his LUE and CT head showed no evidence of hemorrhage. Since it was within window period of National Institute of Neurological Disorders and Stroke (NINDS) criteria, pt received t PA with neurologist consultation. Following thrombolysis pt regained power in his LUE but still had numbness and weakness at left wrist. Later pt was transferred to tertiary care for further workup. Pt was investigated with MRI brain without contrast which revealed findings consistent with acute ischemic infarction in the right occipital horn and to a lesser degree the posterior right parietal lobe with no significant mass effect or hemorrhage. MRA of circle of Willis showed normal variation with absent P1 on the left. Carotid doppler showed 59% stenosis involving bilateral internal carotid arteries. 2D echo showed ejection fraction of 55%, no thrombi with mild left ventricular diastolic dysfunction. Pt was noted to have Acute kidney injury (AKI) on CKD3 with Scr 3.7 from baseline around 2mg/dl.Pt was discharged home with Aggrenox 200/25 mg twice a day, blood pressure meds, Lipitor 40mg daily, physical therapy and to follow up with his nephrologist. On output follow up in 3 weeks, blood work showed worsened renal function with s cr around 10mg/dl with acceptable BP and eosinophilia of 7% with absolute eosinophil count of 0.73x 10-3/mcL (Normal 0.15 – 0.6); urinalysis was yellow in color, bland except 1+ protein with no hematuria or casts. Urinary Eosinophil was negative. Serum lactate dehydrogenase was high 357 unit/L (Normal 100-190). Complement levels were not checked. ANCA titers were negative. Pt denies fever, cola coloured urine, skin rashes, vision loss, flank pain or toes discoloration. So pt was admitted for evaluation of AKI with possible etiology of AERD with or without allergic interstitial nephritis due to Aggrenox. Pt didn't have telltale signs of systemic embolization including skin and gastrointestinal tract. Since there was no significant improvement in renal function, pt was submitted for kidney biopsy. Kidney biopsy revealed fresh cholesterol embolization (fig 1) with marked arteriosclerosis, moderate to severe nephrosclerosis and tubulo-interstitial fibrosis of 50-55%. Patient was treated conservatively with maximum atorvastatin 80 mg daily and is being continued on intermittent outpatient dialysis thrice a week.

Discussion

CKD is associated with an increased risk of stroke. The systemic vascular disease process seen with reduced renal function may partly explain its association with stroke [7].The Atherosclerosis Risk in Communities (ARIC) study assessed the effect of CKD (creatinine clearance [CrCl] <60 ml/min) and anemia on the risk for incident stroke [8]. This study found that a low CrCl was associated with a substantial risk for stroke in the presence of anemia (HR 5.43) and only a modest increased risk in the presence of normal hemoglobin (HR 1.41) [8]. Findings imply that presence of CKD alone should not be a contraindication to administration of intravenous t PA to eligible patients with ischemic stroke from a hemorrhagic risk standpoint [9].

The accelerated progression of atherosclerosis in this population, which may begin during advanced CKD, can be related to a number of factors that are unique to advanced kidney disease, namely elevated calcium-phosphate product, hyper homocysteinemia, inflammation, oxidative stress, and anemia [8,10]. CKD stages 3 to 4 are linked with a higher frequency of atherosclerosis and thrombotic vascular complications; while platelet dysfunction (higher risk of bleeding) has largely been described only in patients with uremia such as in CKD stage 5 [11,12]. No study has reported safety and efficacy of

thrombolytic therapy in patients withCKD presenting with aIS due to perceived high complication rates in CKD, unclear therapeutic efficacy, exclusion from clinical trials or therapeutic nihilism. But Varun et al study revealed CKD presenting with aIS had similar complications of intra cranial hemorrhage (ICH), death similar to pts without renal dysfunction [13].

Cholesterol plaques can dislodge following thrombolytic therapy and does CKD potentiates this risk need to be studied as CKD itself in an inflammatory state. Our index patient had cofounding risk factors for atheroembolic renal disease (AERD) which included atherosclerotic vascular disease, CKD 3, hypertension, hyperlipidemia and smoking. And as noted in literature AERD is under diagnosed kidney disease entity hence labelled as great masquerader [14]. Biopsy study by Jones and Iannaccone reported an incidence of 1.1% [15]. Observed incidence of AERD in clinical practice seems to have increased due to clinical awareness, prolonged survival with atherosclerotic vascular disease, increased invasive procedures, routine usage of thrombolytics and anticoagulants [16]. The Need of tissue biopsy for definite diagnosis underestimates the true prevalence of AERD.

Our patient recovered completely from LUE weakness following thrombolysis, but AERD resulted in ESRD requiring hemodialysis thrice a week to date. Even though biopsy revealed hypertensive nephrosclerotic changes of CKD 3, hadn't been AERD pt would have few years to spare from renal replacement therapy. The dichotomy of the benefit and risk of thrombolysis needs to be challenged. Does this discourage from using thrombolytics in aIS in renal failure, probably not. Again it urges to revisit the plaque stabilization effect of statins in CKD patients. Does the inflammatory, vascular calcification and oxidative state of CKD promote dislodgment of embolization need to be explored? To overcome these deficits larger prospective study is needed to evaluate the safety measures of thrombolytics in advanced renal failure and measure the comorbidity benefits. Also the pharma logical benefits of anti-oxidants, anti-inflammatory, phosphate binders or statins in plaque stabilization need to be explored. Despite with advances the lack of specific therapy for AERD dampens the outcome.

To conclude, AERD the most underdiagnosed disease due to complexity and the need of tissue biopsy to confirm results in under reporting. But the risk of AERD involved with thrombolytic therapy for aIS in CKD should not detain from using t PA. The oxidative stress, metabolic bone disorder, inflammatory activity of CKD may potentiate atheromatous plaques dislodgment. But future endeavors to overcome these paucities are awaited.

Figure

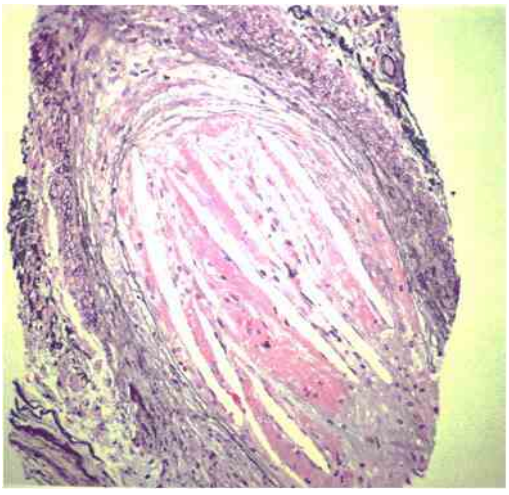

Figure 1: Artery with Cholesterol emboli (Jones' X 100)

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