Recurrent episodic acute kidney injury as presenting manifestation of mitochondrial myopathy

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ABSTRACT

Mitochondrial cytopathies (MC) are a rare heterogenous group of disorders with frequent multisystem involvement including uncommon renal manifestations. Acute kidney injury (AKI) as the primary manifestation of MC is extremely rare. Here, we report a case of recurrent episodic AKI in an adult male who was subsequently diagnosed to have mitochondrial disease.

Key words: Acute kidney injury, mitochondrial myopathy, myoglobinuria, rhabdomyolysis

Introduction

Mitochondrial cytopathies (MC) are a rare and complex group of neuromuscular diseases due to a defect in the oxidative phosphorylation (OXPHOS) system. Symptomatic renal involvement in MC has been documented in the form of tubular defects (complete De Toni-Debré-Fanconi syndrome in severe cases to incomplete proximal tubular defects in milder cases), chronic tubulointerstitial nephritis, cystic renal diseases, rare glomerular diseases such as focal segmental glomerulosclerosis due to 3243 A >G tRNALEU mutations and coenzyme Q10 biosynthesis defects, hypermagnesuria and myoglobinuria.[1,2] Acute kidney injury (AKI) as the sole presenting manifestation of clinically latent MC is extremely rare. We report a case of recurrent episodic AKI caused by exercise induced rhabdomyolysis in a patient whose muscle biopsy revealed the diagnosis of mitochondrial myopathy (MM).

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Case Report

A 53-year-old man presented with the complaints of oliguria, generalized bodyache and dark colored urine. He gave an unusual history of three previous episodes of similar symptoms in the past, at 25, 36 and 48 years of age. He had been treated with peritoneal dialysis during the first episode and hemodialysis in the next two, following which he made a complete recovery. All the four episodes had been preceded by a history of walking long distances prior to the onset of symptoms. He was completely asymptomatic in the interim periods. There was no relevant drug or family history.

On examination, there was no peripheral edema and his blood pressure was 130/80 mmHg, pulse rate was 100/min and systemic examination did not reveal any abnormality. He had no neurological deficits and his muscle strength was normal.

His laboratory parameters during the present episode were as follows: serum creatinine 10.2 mg/dl, blood urea 160 mg/dl, serum sodium 128 mEq/l, serum potassium 6.1 mEq/l and serum bicarbonate 17 mEq/l. His packed cell volume was 36%, total white blood cell count was 5000 with normal distribution and no abnormalities detected on peripheral smear examination. The platelet count was 190,000. His liver function tests showed serum glutamic oxaloacetic transaminase of 2005 IU/l and serum glutamic pyruvic transaminase 880 IU/l. His lactate dehydrogenase was 3310 IU/l and uric acid level was 9.2 mg/dl. Serum creatine phosphokinase was markedly raised, i.e., 35,640 IU/l. Review of previous laboratory

findings also showed a similar pattern. Urine examination revealed the presence of myoglobin. His blood chemistry and urinalysis were consistent with rhabdomyolysis.

The patient underwent three sessions of hemodialysis and attained complete recovery of his renal function. In view of his clinical history and laboratory data, a provisional clinical diagnosis of metabolic myopathy possibly McArdle's disease causing exercise induced rhabdomyolysis was considered and a muscle biopsy was performed. Histopathology revealed skeletal muscle fibers with preserved fascicular architecture and no evidence of necrosis or inflammation. Cryostat sections stained with modified Gomorri trichrome stain revealed characteristic ragged red fibers (RRF) which on histochemical staining showed intense reaction in subsarcolemmal zone for succinic dehydrogenase and nicotinamide adenine dinucleotide tetrazolium reductase. Electron microscopy confirmed the presence of abnormal aggregates of mitochondria in the subsarcolemmal region corresponding to RRF. Adenosinetriphosphatase stain showed normal mosaic pattern. There was no deficiency of myophosphorylase. A final diagnosis of MM was established based on light microscopy, enzyme histochemistry, special stains, and electron microscopy findings.

The patient was evaluated for other systemic manifestations of mitochondrial disease including progressive external ophthalmoplegia, cardiomyopathy, encephalopathy, hypogonadism, and motor neuron disease, which were negative. Screening of immediate family members did not reveal any positive findings. He was counseled regarding his disease condition and urged to refrain from strenuous physical exercises. He has been compliant and on regular follow-up for the last 10 years with no further recurrence of symptoms.

Discussion

Over the last decades, there has been immense development in the field of mitochondrial diseases with an ever expanding list of pathogenic mitochondrial and nuclear DNA mutations causing a wide spectrum of clinically manifest diseases.[3] Since the central nervous system and muscle are frequently involved in mitochondrial diseases, the term mitochondrial encephalomyopathy is commonly used. There are over 40 known syndromes resulting from mitochondrial defects.[4] Acute renal failure is uncommon in mitochondrial diseases and it is extremely rare as a presenting manifestation of the disease.[5] Among the various syndromes associated with mitochondrial diseases, isolated myopathy due to defects in OXPHOS, fits the clinical picture in this patient as he has no other systemic manifestations.

The OXPHOS system, which is embedded in the inner membrane of the mitochondria, is constituted by five enzyme complexes, encoded by two separate genomes, viz., nuclear and mitochondrial. Mutations in the nuclear DNA show Mendelian inheritance whereas primary mitochondrial DNA mutations are sporadic or show maternal inheritance as mitochondrial DNA is only transmitted from mother to child. MM may also be acquired, as in the case of antiretroviral therapy for human immunodeficiency virus infection.[6,7] To the best of our knowledge, this is the first report from India of isolated MM in an adult patient presenting as recurrent episodic AKI.

Irrespective of cause of mitochondrial dysfunction, exercise induced adenosine triphosphate depletion results in intracellular calcium accumulation and myocyte death or rhabdomyolysis, which causes acute renal failure by release of muscle cell contents, especially myoglobin into circulation. Myoglobinuria occurs when myoglobin exceeds 250 ng/ml (normal 5 ng/ml) and causes cast formation and accumulation of iron in proximal tubules. AKI ensues due to direct nephrotoxicity of myoglobin as well as its conversion to ferrihemate at a pH <5.6 which is toxic to renal tubules. In addition, generation of oxygen free radicals and sequestration of fluids in injured muscles results in volume depletion, aciduria, nitric oxide depletion, and renal hypoperfusion further contributing to acute tubular necrosis.[8]

AKI induced by rhabdomyolysis can occur in varied clinical settings such as crush syndrome, trauma, drug overdose, hyperthermia, alcohol abuse, etc.,[9] hence careful collation of history, clinical presentation and laboratory data are required to ascertain the etiology. Recurrent episodic AKI is characteristic of rhabdomyolysis and heightened awareness of the possibility along with appropriate sensitivity to abnormal laboratory values is necessary to reach the diagnosis, which can be corroborated by muscle biopsy when indicated.

The diagnostic workup of renal MC involves amalgamation of multiple modalities, viz., enzymology and biochemistry analyses including measurement of urine organic acids by gas chromatography/mass spectrometry, molecular genetics, pathology (histology, histochemistry, and electron microscopy) and neuroradiology studies, possibly coupled with magnetic resonance spectroscopy.[1,10] In infants, invasive biopsies can be avoided by studies on cultured skin fibroblasts. Renal biopsy findings include mitochondrial abnormalities in proximal tubules and podocytes.[11] Podocyte mitochondrial abnormalities demonstrated

by electron microscopy are highly evocative of CoQ10 defects in early onset steroid resistant nephrotic syndrome, which is a treatable MC.[12,13]

Conclusion

Patients with recurrent rhabdomyolysis related AKI should be further evaluated by means of muscle biopsy. A diagnosis of MM warrants counseling of the patient regarding avoidance of physical stresses which may provoke relapses of the disease. Conversely, screening for subclinical renal involvement and monitoring for renal disorders is required in all patients with MC. Screening of family members, keeping in mind possible maternal as well as Mendelian pattern of inheritance is also important. This case is reported not only for its unusual presentation of a rare disorder, but also to highlight the value of reaching a correct etiological diagnosis of AKI which can lead to prevention of further episodes of renal failure by counseling and institution of appropriate avoidance measures.

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