A Rare Cause of Myoclonus
A Cupric Conundrum

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Report of a Case

An engineering student aged 22 years presented with a 3-year history of jerks when brushing her teeth and a tremor when carrying drinks. There was no family history of tremor and no alcohol response. She had a half-brother with epilepsy. Her parents were not related. Her only medication was the oral contraceptive pill. Examination revealed a bilateral jerky tremor, stimulus-sensitive myoclonus, and difficulty with tandem gait. Thyroid and liver function test results were normal, but she had rapidly progressive renal failure. Serum copper, ceruloplasmin, and manganese levels were normal, but her urinary copper level was elevated on 2 occasions. Pathological findings on organ biopsy prompted genetic testing to confirm the diagnosis. The differential diagnosis, tissue biopsy findings, and final genetic diagnosis are discussed.

Laboratory and Imaging Studies

Thyroid and liver function test results were normal, but renal function was impaired (urea level: 32.21 mg/dL [normal range, 7-22 mg/dL]; creatinine level: 2.36 mg/dL [normal range, 0.6-1.2 mg/dL]; and estimated glomerular filtration rate: 26 mL/min/1.73 m²). Autoantibody and vasculitic screens were negative. There were no acanthocytes on a thick blood film. Full blood picture revealed mild eosinophilia; her erythrocyte sedimentation rate was elevated at 81 mm/h (to convert to mm/h, multiply by 0.015). Serum copper, ceruloplasmin, and manganese levels were normal, but her urinary copper level was elevated on 2 occasions (135 and 196 μg/24 h [normal range, 3-35 μg/24 h]). Urinary albumin excretion was high; the albumin-creatinine ratio was 3398 mg/g (nephrotic range) with associated hypoalbuminemia. Electroencephalogram and magnetic resonance imaging of brain and DaTscan were normal.

Clinical Discussion (Dr Forbes)

The phenomenon of the movement disorder was a jerky tremor with stimulus-sensitive myoclonus. We were told tandem gait was difficult, which may suggest cerebellar dysfunction. Although the tremor was jerky, it was not typical of a coarse rubral tremor, and there was no significant dysmetria. It was possible there was subtle dystonic posturing of her hands (“dinner fork”), but there did not appear to be any task-specific dystonia in the form of writer’s cramp and no evidence of torticollis. I thought we were predominantly dealing with myoclonus but also possibly with cerebellar dysfunction.

The presentation of a hyperkinetic movement disorder in a young patient always prompts consideration of Wilson disease, and her presentation with a tremor (although not “wing-beating”) and a disturbance of gait would make this a reasonable thought. Normal ceruloplasmin levels and the absence of Kayser-Fleischer rings would be fairly strong evidence against a neurological presentation of Wilson disease, but instances in which patients are negative for Kayser-Fleischer rings but positive for neurological Wilson disease are known, although very rare. The normal ceruloplasmin level may be a false-negative explained by use of the oral contraceptive pill, which causes a rise in serum ceruloplasmin levels.

The unanticipated finding of renal failure and nephrotic range proteinuria was likely tied into the diagnosis in a more meaningful way, but renal failure of any cause can produce myoclonus as part of an encephalopathic state, although this would be very uncommon at this level of renal dysfunction. There are many conditions in which renal disease and neurological disease can coexist, but not many will have a hyperkinetic movement disorder as a key feature. Renal failure is not typical of Wilson disease, although renal stones...
can be a feature. A vasculitic disorder manifesting with cerebral and renal dysfunction needs to be excluded given the elevated erythrocyte sedimentation rate and eosinophilia, although patients who present with cerebral vasculitis are usually acutely and severely ill. Her brother has epilepsy, which may be relevant if we are dealing with an inherited disorder, but none of the major inherited myoclonic epilepsies (ie, Lafora body disease, Unverricht-Lundborg disease, and neuronal lipofuscinosis) are commonly accompanied by renal failure. Other rare genetic cerebrorenal diseases (eg, Lowe syndrome and Mowat-Galloway syndrome) will be accompanied with clear features of dysmorphism from infancy. Mitochondrial disorders must always be on a neurologist’s differential diagnosis of multisystem disease. There are mitochondrial phenotypes that could manifest as a myoclonic disorder (eg, myoclonic epilepsy, myopathy, and sensory ataxia; and myoclonic epilepsy with ragged red fibers), and renal disease is a recognized manifestation of mitochondrial disease.

If the high renal copper excretion, renal failure, and proteinuria were not due to Wilson disease, vasculitis, or mitochondrial disorders, then we may be left with the possibility of a very rare inherited disease called action myoclonus renal failure syndrome (AMRFS), which can present with a myoclonic syndrome or renal impairment. Most patients will have proteinuria and (unlike our patient) an abnormal electroencephalogram. The pathological hallmark on renal biopsy is collapsing focal and segmental glomerulosclerosis (FSGS). Given this was a pathological case, I suggest that this is where the diagnosis was made. My proposed diagnostic test would be a renal biopsy to identify either FSGS, vasculitis, or to identify a mutation in mitochondrial DNA.

Clinical Progression

Initially, the patient reported reduction in jerks while receiving clonazepam. Unfortunately, a few months after recognizing renal impairment, she developed severe fatigue and was found to be hypertensive and anemic and had clinical features of nephrotic syndrome (ie, peripheral edema, hypoalbuminemia, and proteinuria). Her kidney disease rapidly progressed, and she underwent renal biopsy.

Pathological Discussion (Dr Gray)

On light microscopy of the renal cortex, 6 glomeruli were identified, of which 3 were completely sclerosed. There were extensive foci of segmental sclerosis, sometimes more than 1 segment per glomerulus, with hyalinosis within the sclerosed segments. There was podocyte hyperplasia overlying some of the sections, and some of the capillary tufts were shrunken with sclerosis at the hilum (Figure). The pattern was typical of FSGS, and although there were some collapsing features, the pattern was not definitively one of the collapsing variant.

The capillary basement membranes were not thickened; there were no silver-positive spikes or double contours. There was widespread tubular epithelial vacuolation, almost certainly associated with proteinuria. There was no crystalline material in the tubular epithelium. There was focal regenerative activity. Some of the tubules were small and atrophic. There was mild and focal inflammation in the interstitium and mild to moderate interstitial fibrosis. Some fibrinoid deposits were present in small arteries. On immunofluorescence, there was irregular positivity in the glomeruli for complement components 3 and 4. Immunoglobulin M was present in some glomerular segments, but the appearances were nonspecific and not that of immune complex–mediated disease. Ultrastructural examination of the glomeruli confirmed FSGS-like changes (extensive sclerosis with associated widespread foot-process effacement).

Clinical Outcome

The combination of rapidly progressive chronic kidney disease due to FSGS and action myoclonus prompted further detailed genetic testing for mutations in the SCARB2 gene (OMIM 602257) and other genetic causes of FSGS using a 37-gene renal panel. The patient was found to be compound heterozygous for SCARB2 pathogenic variants (c.434_435 duplication in exon 4 and splice site variant c.704+5G>A in intron 5), strongly supporting the diagnosis of AMRFS, also known as myoclonic nephropathy or progressive myoclonic epilepsy (PME) type 4.

Examination of the renal cortex revealed focal segmental glomerulosclerosis. Some glomeruli were completely sclerosed (yellow arrowhead [B]), while others had foci of sclerosis as seen in the perihilar region (white arrowheads). Partial collapse of the capillary tuft (blue arrowhead [A]) separates it from the basement membrane. Both images are from the same field (left panel, hematoxylin-eosin [A]; right panel, silver staining [B]).
Her renal function continued to deteriorate rapidly, and she commenced continuous ambulatory peritoneal dialysis for end-stage renal disease 3 months after biopsy. She found this self-care dialysis technique difficult, as her jerks often caused her to drop the sterile equipment, and the process required repeated attempts and often help to perform the necessary aseptic steps for safe dialysis. Her mother was assessed as a potential live kidney donor, and the patient underwent kidney transplantation within 2 months of starting continuous ambulatory peritoneal dialysis. She had primary kidney transplant function, and by day 5 after transplant, her serum creatinine levels were within normal range at 1.03 mg/dL, and the clinical features of nephrotic syndrome were resolved. She is now treated with an immunosuppressive regimen consisting of tacrolimus, mycophenolate mofetil, and prednisolone. Unfortunately, despite normal renal function and an initial response to clonazepam, her movement disorder has progressed, and she reports worsening balance (Video 2). This may be partly due to tacrolimus toxicity. She remains free of seizures, and despite persisting neurological difficulties, she hopes to start work as an engineer in the near future.

Conclusions

In 1986, AMRFS was first recognized and accurately described in 4 French-Canadian patients from 3 families and was later followed by a large case series that demonstrated autosomal recessive inheritance. Patients aged 17 to 26 years presented with a tremor of the fingers or hands and with myoclonus at 14 to 29 years, and most also had infrequent generalized seizures (73% of patients presented at a mean age of 23 years). Cerebellar features, including dystarthria, pendular reflexes, rebound, and nystagmus, were found in some patients. Renal failure followed the development of proteinuria in 12 of the 15 cases at a mean interval of 4 years. Two patients were examined post mortem, and neuropathological study revealed extraneuronal storage material in the cerebral and cerebellar cortices, globus pallidus, and putamen without significant neuronal loss. The renal biopsy picture was that of collapsing glomerulopathy. Nine of the patients described died (mean age, 30 years) of renal failure, complications of renal replacement therapy, or respiratory compromise related to their progressive neurological syndrome.

The SCARB2 gene, which encodes the lysosomal integral membrane protein 2 (LIMP2), was identified in 2008. Although less abundant than lysosomal-associated membrane proteins 1 and 2, LIMP2 has a function in general lysosome maintenance and acts as a receptor for several strains of enteroviruses and coxsackieviruses. It also transports glucocerebrosidase to lysosomes and may contribute to the phenotypic heterogeneity of Gaucher disease.

Study of LIMP2 knockout mice initially suggested a clinical and pathological picture that differed from patients with AMRFS. Mice deficient in LIMP2 were described as having hearing loss, peripheral demyelinating neuropathy, and an ataxic gait but not the myoclonus or epilepsy seen in humans with SCARB2 mutations. The pathological lesions in the LIMP2 knockout model also differed from human diseases with a renal phenotype of ureteropelvic junction obstruction (possibly an effect of accumulation of lysosomes in epithelial cells of the ureter adjacent to the ureteral lumen) and brain findings of intracellular inclusions in cerebral cortex and Purkinje cells. Recently, the spectrum of human disorders caused by SCARB2 mutations has expanded to include severe PME without renal failure mimicking Unverricht-Lundborg disease, PME with hearing loss, PME with demyelinating peripheral neuropathy, and PME with dilated cardiomyopathy. Badhwar et al suggested that the myoclonus, seizures, and ataxia in AMRFS may be the result of the extra-neuronal storage material found on neuropathological study on an as-yet-unknown physiological system akin to other PMEs that have intraneuronal storage material (e.g., Lafora body disease and sialidosis). They also hypothesized that the absence of similar storage material on postmortem study of the kidney reflected clearance of the mutant protein.

Pathogenic variants of SCARB2 have differing cellular effects, depending on the cell line of interest. For instance, mutated SCARB2 still permits formation of normal lysosomal structure in fibroblasts but leads to the formation of autophagosomes in lymphoblastoid B cell lines. These in vitro studies and the varied clinical phenotypes associated with the described SCARB2 mutations suggest that LIMP2 protein interactions will cause a variety of pathophysiological effects that are cell- and tissue-specific.

Although rare, myoclonic Wilson disease has been described, but this was not a case of myoclonic Wilson disease. The elevated copper excretion reflected the excess loss of copper-binding proteins because of the nephrotic syndrome (the 24-hour urine collection measured both free and bound copper), highlighting the importance of quantifying total proteinuria when measuring urinary copper excretion in patients being investigated for Wilson disease. Nephrotic syndrome also explains the elevated erythrocyte sedimentation rate. Patients with very advanced renal disease can present with neurological features secondary to uremic encephalopathy, but the movement disorder was present in this patient prior to the development of renal impairment on retrospective review of renal indices, and it progressed despite adequate renal replacement therapy.

This is the first patient from the United Kingdom or Ireland with AMRFS, and her compound heterozygote state was caused by 2 previously recognized variants. The c.434_435duplication has been previously shown to result in a truncated protein, which is unable to bind glucocerebrosidase. The c.704 + 5G > A splice site variant, although not yet studied in vitro, has been previously reported in a patient with AMRFS in a compound heterozygous state and splice site prediction tools show this variant may affect the normal splicing of SCARB2 exon 5. Both variants are also very rare in the European population, according to the Exome Aggregation Consortium database (c.434_435 duplication, 0.012%; c.704 + 5G > A splice variant, 0.0015%), which further supports their pathogenicity.

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REFERENCES