Case Report

# Membranous Nephropathy in a Patient with Charcot-Marie-Tooth Disease: Association of Myelin Mutations


## Abstract

A 40-year-old female presented to the neurologist with gradually progressive weakness of distal and proximal muscles of both lower limbs and cramps for 2 years. She gave a history of similar illness in her paternal grandmother and her father. Her examination revealed bilateral foot drop and mild proximal muscle weakness. She was diagnosed to have peripheral neuropathy and subsequently treated conservatively. Over the next year, she noticed progressive swelling of both lower limb and frothy urine. A nephrology consultation was obtained, and a renal biopsy was done, which showed membranous nephropathy. She was started on steroids and subsequently on tacrolimus as the proteinuria progressively worsened. Her anti-phospholipase A2 receptor antibody was negative both in blood and in the kidney biopsy tissue. A search for a genetic basis of this rare clinical condition was made, and heterozygous mutation was detected in the myelin gene. This mutation was confirmed with genetic sequencing. The mutation is associated with MPZ gene and is associated with multiple hereditary sensorimotor neuropathy. MPZ knockout mice have been shown to have increased glomerular permeability and proteinuria.


**Keywords:** *Charcot-Marie-Tooth disease, membranous nephropathy, MPZ mutations, proteinuria*


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## Introduction

Membranous nephropathy has been associated with various secondary causes. Recent use of the antiphsopholipase A2 antibody levels often help discriminate between the primary and secondary causes of membranous nephropathy. We report a case of secondary membranous nephropathy associated with a type of hereditary sensorimotor nephropathy. We also speculate that the mutation detected is associated with both the neural and renal manifestations in this patient.

## Case Report

A 40-year-old female born to a non consanguineous marriage, mother of one child, presented to a neurologist with progressive change in gait and muscle weakness of 2 years duration. Historically, she found it difficult to clear hurdles. She also had a history of leg muscle cramps. She was seen by the neurologist, who thought it to be a neuropathy. Her magnetic resonance imaging of brain and spinal cord was normal. Her cerebrospinal fluid study was also normal. Her nerve conduction studies were suggestive of sensorimotor demyelinating neuropathy. As she had a family history of similar neurological illness, a form of hereditary sensorimotor neuropathy was considered. Routine investigations at that time had not revealed any renal abnormality. She was started on multivitamins and gabapentin for her cramps. She was asked to follow-up, but due to personal reasons, she did not meet her neurologist subsequently. After 1½ year of her muscle weakness, she started developing progressive bilateral leg swelling. She initially attributed this to her neurological illness and only sought nephrology consultation when she noticed that she was passing frothy urine. Investigations revealed the presence of normal renal functions and nephrotic range proteinuria. Her abdominal ultrasound revealed normal-sized kidneys with normal echotexture. A renal biopsy was performed. Hematoxylin and eosin-stained slides showed congested capillaries with rigid capillary walls [Figure 1]. There were no proliferative lesions. The capillaries revealed uniform basement thickening with Periodic acid–Schiff staining [Figure 2], and few spikes were noted giving the capillary a fuzzy appearance on silver



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staining [Figure 3]. The electron microscopy revealed normocellular glomeruli with foot process effacement. Few subepithelial and intramembranous electron dense deposits were seen [Figure 4]. A diagnosis of early membranous nephropathy was made. Tissue immunohistochemistry for phospholipase A2 receptor antibody on the renal biopsy specimen came negative. Given the clinical and histopathological presentation, a diagnosis of secondary membranous nephropathy was considered.[1-3]

Because of a sensory motor neuropathy which appeared to be hereditary in nature, it was decided to look for mutations associated with inherited neuropathies.[4] A heterozygous nonsense variation in exon 2 of the MPZ gene (chr 1:1612777077; G>G/A; Depth 105x) was identified. This was later confirmed with genetic sequencing [Figure 5]. The MPZ mutation is believed to be predominantly associated with Charcot-Marie-Tooth disease type 1b (a type of hereditary sensorimotor neuropathy). A diagnosis of secondary membranous nephropathy associated with Charcot-Marie-Tooth disease type 1b (OMIM#118200) was made.[5] She was initially started on steroids (1 mg/kg/day) and her proteinuria was monitored. Despite therapy for >6 weeks, the proteinuria worsened. She was started on tacrolimus (0.05 mg/kg/day) and her proteinuria started to improve [Table 1]. Six months on tacrolimus, she is on clinical and biochemical remission.

## Discussion

Membranous nephropathy is one of the major causes of nephrotic syndrome in adults. Most commonly it is idiopathic, but a certain percentage are secondary in nature.[5,6] The major groups of diseases that underlie membranous nephropathy are infections (hepatitis B, hepatitis C, malaria, and schistosomiasis),[7,8] autoimmune diseases (SLE, rheumatoid arthritis),[9] malignancies,[10] and drugs (captopril, penicillamine, gold, carbamazepine etc.,).[11] Various other unusual associations with membranous nephropathy have also been reported in literature.[12,13]

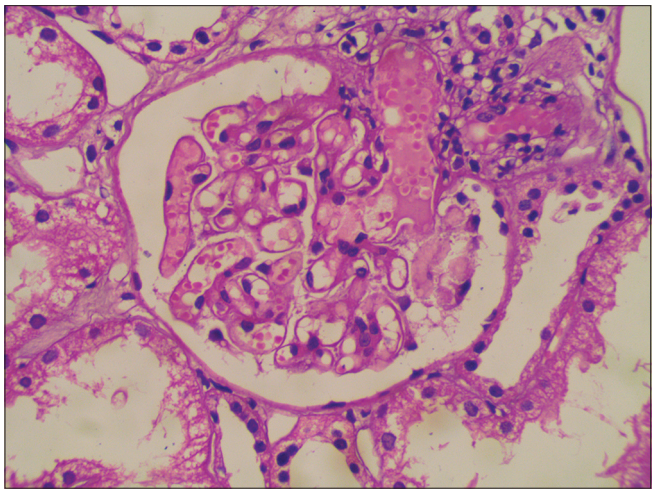

**Figure 1: Capillary lumina rigidity with few congested capillary lumina containing red blood cells (H and E, ×40)**

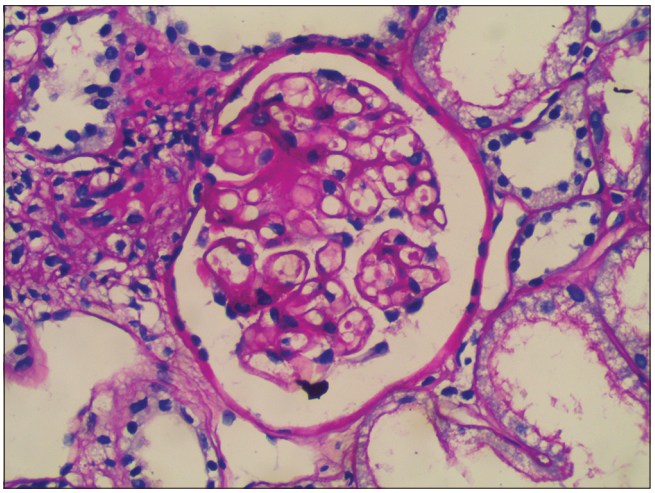

**Figure 2: Uniform and diffuse basement membrane thickening with no increase in cellularity (Periodic Acid Schiff, ×40)**

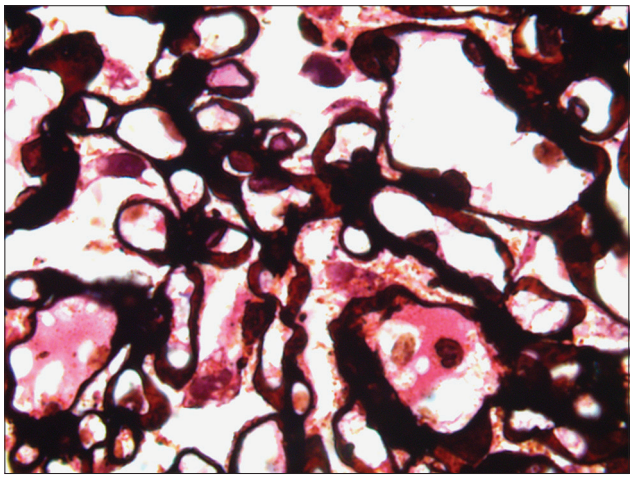

**Figure 3: Capillary basement membrane thickening with few of them showing fine spikes giving the appearance of a fuzzy border (Silver Stain, ×100)**

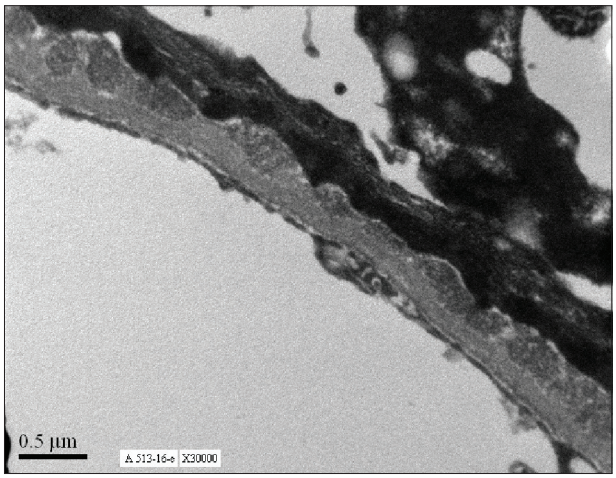


**Figure 4: Electron microscopic image showing foot process effacement and small subepithelial deposits**

**Table 1: Urine routine and urine protein creatinine ratio and the impact of treatment**

| Urine protein | Date | | | | |
|---|---|---|---|---|---|
| | 11/07/2014 | 30/3/2016 (Renal biopsy and initiation of steroids) | 05/2016 (Steroids tapered and tacrolimus started) | 15/07/2016 | 16/12/2016 |
| Urine protein (routine investigation) | Absent | ++ ( 1g/l) | ++++ ( >20g/l) | + (0.3g/l) | Absent |
| Urine protein creatinine ratio | Not done | 2.6 | 11.3 | 1.3 | 0.08 |

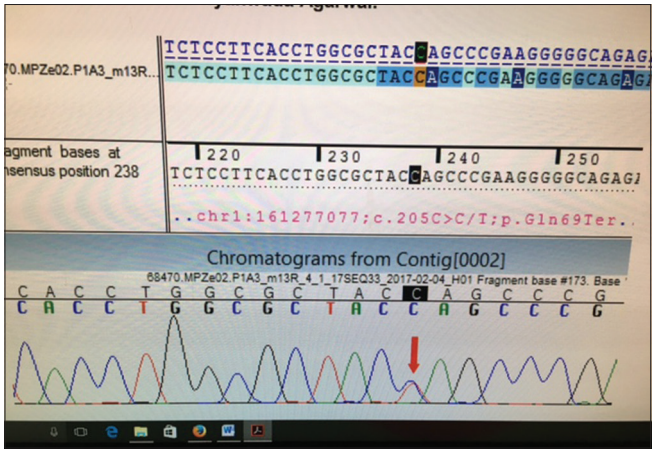


**Figure 5: Genetic sequencing showing the presence of MPZ mutation**

Sporadic cases of hereditary sensorimotor neuropathy and proteinuric illness have been reported in literature. The histopathology in these cases has been either minimal change disease or focal segmental glomerulosclerosis (FSGS).[14-16] These reports have also mentioned human leukocyte antigen associations in these cases. Over the last decade, the role of various mutations in Charcot-Marie-Tooth disease is being elucidated and subtyping-based mutations are increasingly reported in literature. Central to this is the association of mutations coding for myelin genes and Charcot-Marie-Tooth disease.[4] MPZ (Myelin protein 0 or P0) mutations in mice are responsible for increased glomerular permeability and albuminuria in these affected animals.[17] These authors have shown the presence of myelin protein in human and mouse renal cortex from the earliest phase of glomerulogenesis. The histology in these mice was that of "no change disease" with focal areas of glomerular basement membrane thickening, as described by the authors.

Heterozygous mutations in the myelin protein (MPZ) in humans are detected in Charcot-Marie-Tooth disease type Ib. We speculate that the presence of MPZ mutations in this patient is responsible for both the renal and neurological clinical manifestations. Further research in the localization of myelin protein in the glomerulus and its pathogenetic role will elucidate its importance in proteinuric illnesses in humans.

## Conclusion

Membranous nephropathy with hereditary sensorimotor neuropathies has been reported. We believe that the link between membranous nephropathy and Charcot-Marie-Tooth disease is the presence of the MPZ mutation.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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