

## Nephritis and Charcot-Marie-Tooth Disease: An Unusual Association

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### ABSTRACT

A 24 years old male, who presented to us with uraemic symptoms secondary to chronic glomerulonephritis. On examination, he was found to have features of peripheral neuropathy which was confirmed as Charcot-Marie-Tooth type 1 on nerve conduction studies. Very few cases of glomerular disease, mainly focal segmental glomerulosclerosis have been associated with the Charcot-Marie-Tooth worldwide.

**Key words:** Charcot-Marie-Tooth disease. Glomerulonephritis. Uraemia. Peripheral neuropathy. Focal segmental glomerulosclerosis.

### INTRODUCTION

Charcot-Marie-Tooth disease type 1 is a hereditary degenerative disorder, with motor and sensory neuropathies, which are mainly characterized by muscle weakness and wasting, foot deformities, and electrophysiological, as well as histological changes. Professor Jean Martin Charcot of France (1825-1893) and Pierre Marie (1853-1940) published the first description of the disease in 1886, calling it peroneal muscular atrophy. Howard Henry Tooth (1856-1926) was the first to attribute symptoms correctly to neuropathy rather than to myelopathy.

Charcot-Marie-Tooth disease has been classified into several types on the basis of genetics. It has been associated with nephritis only in a few number of cases worldwide. The pathophysiology explaining both the neurodegenerative disorder and nephropathy has been pointed to mutation in genes for myelin protein O which is found in both myelin sheath of the neurons and podocytes of the nephron.<sup>1</sup> However, in view of the small number of cases reported and lack of advanced studies, the possibility that the association is coincidental and patient has a different disease processes can not be excluded.

This case report describes the unusual association in a young male.

### CASE REPORT

A 24 years old male, tractor driver by profession, non-smoker, and non-addict admitted via emergency in the Nephrology Department of Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan, with 4 months

history of uraemic symptoms. The most prominent symptoms were pruritis for 4 months and episodes of vomiting for 3 months. There had been two episodes of epistaxis, nocturia for 7 months, anorexia and weight loss for 3 months, dyspnoea, orthopnoea and paroxysmal nocturnal dyspnoea for the last one-month and oliguria for one week. There were no mouth ulceration, alopecia, joint pains, photosensitivity, or haematuria. He was initially managed in District Hospital Mirpur where he was found to have anaemia and markedly elevated serum creatinine (14.0 mg/dl) and blood urea (329 mg/dl). On the basis of this patient was labelled as having chronic renal failure and shifted to PIMS. Since childhood, patient had weakness of lower limbs as well as hands. This was slowly progressive to the extent he was not able to drive and write any more. He also had developed deformity of his feet and legs. His father had died of end stage renal disease at the age of 35 years. He had been transfused 2 pints of blood.

Examination revealed a young man mildly pale and tachypnoeic with scratch marks on the whole body with pulse rate of 72/minute, blood pressure of 160/100 mm Hg, and respiratory rate of 18 breaths/minute. JVP was raised. There was no pedal oedema or facial puffiness. His abdominal examination was unremarkable. On CNS examination, he was conscious and fully oriented. Higher mental functions and cranial nerves were intact. Examination of lower limbs revealed atrophy of the distal muscles of lower limbs with pes cavus, bilateral foot drop and Champaign-bottle appearance. On motor examination of lower limbs findings there was bilaterally reduced bulk, fasciculations were present and power was 2/5 bilaterally in distal muscles. Bilateral ankle and knee jerks were absent and planters were downgoing. There were no cerebellar signs. Sensory examination showed loss of position sense upto the ankle on left side and loss of pinprick sensation upto the knee. He also had a high stepping gait.

Blood analysis showed microcytic hypochromic anaemia, with normal leukocyte and platelet count. Serum creati-

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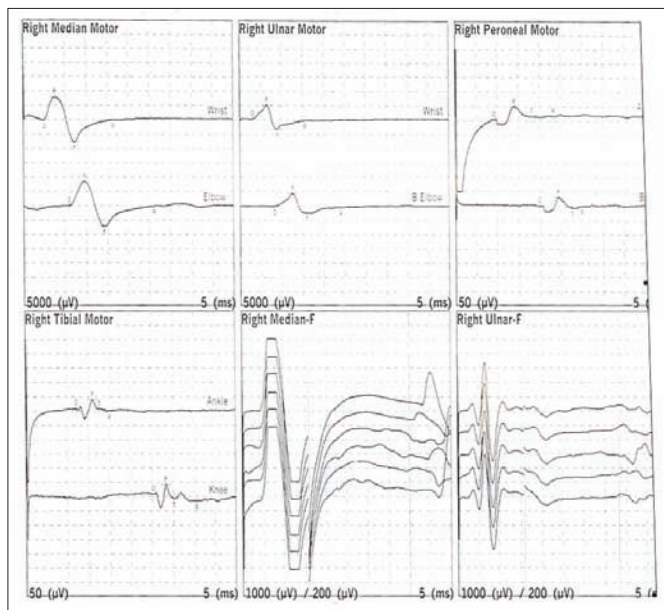
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nine was 24.5 ug/dl and urea was 466 ug/dl. Serum potassium was 4.8 mmol/dl, calcium was 6.4 mg/dl,  $S_2PO_4$  was 11.3 mg/dl and calcium-phosphorus product was 72.3. His random blood sugar level was 118 mg/dl. Urine examine showed protein: 3+, blood: 2+, RBC: 11-12/hpf and WBC: 6-7/hpf. He was HBV and HCV negative. Total proteins were 6.4 mg/dl with albumin fraction of 3.2 mg/dl. Arterial blood gases showed metabolic acidosis with pH of 7. Ultrasound abdomen showed small sized kidneys measuring 82 mm on the right and 84 mm on the left side.

Patient was initially managed on lines of end stage renal disease with haemodialysis, blood transfusion and supportive therapy for chronic renal failure.

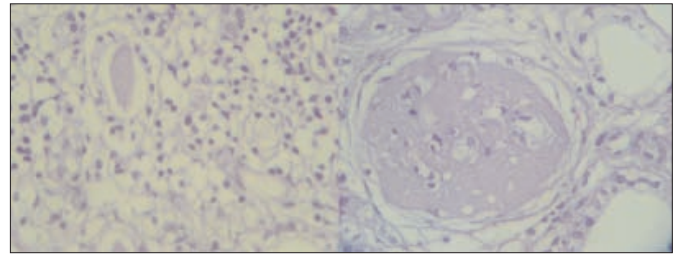
He was further investigated. His ANA, ANCA were negative ruling out the vasculitides. Serum lead levels were normal and peripheral film showed no basophilic stippling hence lead poisoning was excluded as well. Fundoscopy was normal and audiometry showed left sided sensorineural deafness for low frequencies. For the type of neuropathy his nerve conduction studies were done which showed delayed F wave forms, with prolonged distal latencies and markedly decreased distal conduction velocities labelling him as case of Charcot-Marie-Tooth type 1 (Figure 1).



**Figure 1:** NCS shows delayed F-wave markers. The sampled nerves prolonged distal latencies and markedly decreased distal conduction velocities. CMAP was of low amplitude with some degree of dispersion. Consistent with Charcot-Marie Tooth type 1.

Renal biopsy showed sclerosed glomeruli some of them had segmental involvement. There was increased mesangial matrix, thickened membranes were seen at places. Tubules were vacuolated and swollen. Suggesting membranoproliferative glomerulonephritis leading to end stage renal disease (Figure 2).

Patient underwent renal transplant and is being followed-up regularly.



**Figure 2:** Renal biopsy: vacuolated and swollen tubules with sclerosed glomerulus, increased mesangial matrix and fibrosis.

## DISCUSSION

Charcot-Marie-Tooth disease (CMT) is the most common inherited neurological disorder. Slow progressive weakness beginning in the distal limb muscles, typically occurring in the lower extremities before the upper extremities. Patients initially may complain of difficulty in walking and frequent tripping. As weakness becomes more severe, foot drop and high stepping gait is common. Intrinsic foot muscle weakness commonly results in the foot deformity known as pes cavus. Hand weakness results in complaints of poor finger control, poor handwriting, and difficulty using zippers and buttons, and clumsiness in manipulating small objects. Patients usually do not complain of numbness as patients with CMT never had normal sensation and, therefore, simply do not perceive their lack of sensation. Pain, both musculoskeletal and neuropathic types, may be present.

In the originally reported cases of brothers, the nephropathy was characterized by proteinuria, microscopic haematuria and both had nerve deafness.<sup>2</sup> The third patient, a 21-year-old female, unrelated to the first two patients, showed persistent proteinuria.<sup>2</sup> Renal biopsy revealed small foci of tubular atrophy with lymphocytic infiltration or fibrosis in each patient. In one patient diffuse thickening of the glomerular membrane and foam cells in the interstitium were also found. In 1984 another case of 14-year-old girl with Charcot-Marie-Tooth (CMT) disease and the nephropathy which was characterized by heavy proteinuria and microscopic haematuria.<sup>3</sup> Renal biopsy specimens revealed the features of focal segmental glomerulosclerosis (FSGS). In 1985 fifth case of the series was reported a young patient who was admitted with a nephrotic syndrome also had CMT 1.<sup>4</sup> This case reported by a young patient who was admitted with a nephrotic syndrome. A terminal renal failure rapidly developed. Numerous chronic nephropathies were known in the patient's family. The ultrastructural study of the renal biopsy revealed a focal fusion of the epithelial foot processes, thickened and pleated mesangial basal laminae, vacuolated podocytes and small intranuclear clear inclusions. The Charcot-Marie-Tooth disease was of the hypertrophic type.

The outcome of renal involvement has the same profile i.e. proteinuria at onset with or without microhaematuria,

sometimes with nephrotic syndrome. The prognosis is often poor, since 9 out of 13 patients have end-stage renal failure after 6 months to 17 years of follow-up.<sup>5</sup> In 1998 first report of fibrillary glomerulopathy, which is characterized by the widespread deposition of randomly arranged, elongated, non-branching microfibrils in the mesangium and glomerular basement membrane, associated with this neurological disorder was reported in a young man.<sup>6</sup> Like all these cases, our patient was found to have features of Charcot-Marie-Tooth disease and had developed renal failure with renal biopsy showing increased mesangium, and vacuolated tubules. The pathology which links the two disease processes was suggested to be deficiency of myelin protein O.<sup>1</sup> Myelin protein O is a transmembrane glycoprotein that represents the most abundant myelin component in peripheral nerves. Mutations in the PO gene are associated with one form of autosomal dominant demyelinating peripheral neuropathy, Charcot-Marie-Tooth disease type 1B (CMT1B).<sup>7</sup> PO mRNA was detected by reverse transcriptase-PCR in the human and mouse renal cortex.<sup>6</sup> PO transcripts were also identified by in situ hybridization at different stages of the mouse kidney development, especially in embryonic structures that give rise to the glomerulus.<sup>1</sup> Immunofluorescence and immunogold electron microscopy studies on human kidney sections disclosed a predominant staining of the membranes of intracellular vesicles in podocytes.<sup>1</sup> PO-mice exhibited mild growth retardation and demyelinating neuropathy similar to the one observed in patients with CMT1B.<sup>6</sup> They also presented mild albuminuria, without significant ultra structural change of the glomerular basement membrane or the podocytes.<sup>1</sup> These results demonstrate that PO, the major myelin protein, is also expressed during nephrogenesis and in mature kidney, mostly in

podocytes.<sup>1</sup> So this suggests that PO gene mutations might be involved in renal diseases along with the neuropathy.<sup>1</sup>

As the number of cases reported is small, the possibility that the association is purely coincidental cannot be excluded. However, the well-established hereditary nature of Charcot-Marie-Tooth disease and the clinic pathological features of the renal disease present in the patients reported including our patient, and keeping in mind pathophysiology suggested the association of Charcot-Marie-Tooth disease and nephritis may not be a mere coincidence. It might be a separate pathological entity.

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