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Haemodialysis alters peripheral nerve morphology in end-stage kidney disease

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HIGHLIGHTS

- Patients with end-stage kidney disease had larger and more hypoechoic nerves compared to normal controls.
- The degree of nerve enlargement correlated significantly with electrophysiological parameters and clinical severity.
- There was a significant decrease in nerve cross-sectional area and hypoechoic fraction following a single dialysis session.

ABSTRACT

Objective: We explored the nerve ultrasound (US) characteristics of 15 patients with end-stage kidney disease (ESKD) and correlated these findings with clinical severity and electrophysiological parameters of neuropathy.
Methods: 15 ESKD patients on thrice-weekly high-flux haemodialysis and 15 healthy controls were enrolled. Sonographic and electrophysiologic studies were conducted before and after a single session of haemodialysis. Serial measurements of median nerve cross-sectional area (CSA) and hypoechoic fraction (HF) were performed at the same non-entrapment site in the mid-forearm. Neuropathy severity was quantified using the total neuropathy score (TNS).
Results: 86.7% of the ESKD cohort had neuropathy (TNS > 1). ESKD patients had significantly higher baseline CSA (8.9 ± 1.2 mm^2 vs 7.5 ± 1.0 mm^2, $p < 0.05$) and HF (56.0 ± 1.0% vs 54.0 ± 1.1%, $p < 0.05$) compared with the control group. The CSA correlated significantly with TNS ($r = 0.826$; $p < 0.0001$) and other electrophysiological parameters. There was a reduction in both the CSA (8.3 ± 1.4 mm^2; $p < 0.01$) and HF (55.0 ± 1.6%; $p < 0.05$) after a single session of HD. A significant relationship was also found between the change in CSA and change in serum K^+ after dialysis ($r = 0.782$, $p < 0.01$).
Conclusions: This study shows that peripheral nerves in ESKD patients are larger and more hypoechoic and that these morphological abnormalities may be reversed by dialysis.
Significance: US may be useful as an early marker of neuropathy in ESKD.

1. Introduction

Neuropathy is the most common neurological complication of end-stage kidney disease (ESKD) occurring in 60–90% of patients

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(Krishnan and Kiernan, 2009; Hojs-Fabjan and Hojs, 2006; Laaksonen et al., 2002; Van den Neucker et al., 1998). The most prominent clinical features are paraesthesia, numbness, reduction in deep tendon reflexes, impaired vibration sense, muscle atrophy and weakness, which are indicative of damage to large myelinated nerve fibers. Typically, symptoms progress in a length-dependent fashion, with greater lower-limb than upper-limb involvement (Tilki et al., 2009; Krishnan et al., 2009; Krishnan and Kiernan, 2007). Nerve conduction studies (NCS) often reveal a generalized neuropathy which is predominantly axonal with reductions in sensory and motor amplitudes (Krishnan and Kiernan, 2007). Nerve excitability studies, which provide information on axonal ion channel and membrane potential, have been studied extensively in ESKD patients and have shown prominent changes consistent with axonal membrane depolarization (Kiernan et al., 2002, 2000). Further studies have shown that these excitability abnormalities are rapidly reversed after a single session of dialysis (Krishnan et al., 2005, 2006a, 2006b). This is in contrast to traditional NCS which demonstrate minimal change over a dialysis session (Laaksonen et al., 2002).

Despite the wealth of information provided by these studies, there are no studies exploring the changes in nerve morphology that may occur following dialysis in patients with ESKD. A considerable number of studies have evaluated the diagnostic utility of nerve ultrasound (US) as a marker of nerve morphology in mononeuropathies (Borire et al., 2016a,b; Simon et al., 2015; Cartwright et al., 2012), and more recently in acquired and inherited polyneuropathies (Ebadi et al., 2015; Goedee et al., 2013; Gallardo et al., 2015; Grimm et al., 2014; Shen and Cartwright, 2016; Visser and Beekman, 2011; Zaidman et al., 2009). These studies have demonstrated changes in the nerve cross-sectional area, fascicular size and arrangement as well as echogenicity. More recently, a few studies have assessed the sonographic characteristics of metabolic neuropathies, focussing largely on diabetic patients (Arumugam et al., 2016; Watanabe et al., 2009, 2010; Liu et al., 2012; Wei et al., 2012; Riazi et al., 2012). In this prospective study, we examined changes in nerve morphology across a dialysis session in a cohort of ESKD patients. We also explored the correlation of these findings with clinical severity and electrophysiological parameters.

2. Methods

The study was approved by the Human Research Ethics Committee of the Prince of Wales Hospital, Sydney. Written informed consent was obtained from all study participants. This was a blinded, prospective, cross-sectional study of ESKD patients on hemodialysis (HD), recruited from two outpatient dialysis centers in Sydney (Prince of Wales and War Memorial Hospitals). Inclusion criteria comprised of ESKD patients aged 18–85 years, who were able to give informed consent, and who were maintained on hemodialysis for at least 6 months. Patients with a clinical history and/or electrodiagnostic features of carpal tunnel syndrome or previous traumatic median nerve injury were excluded from the study. The causes of ESKD in these patients included focal segmental glomerulosclerosis ($n = 1$), diabetes ($n = 3$), polycystic kidney disease ($n = 2$), IgA nephropathy ($n = 2$), glomerulonephritis ($n = 2$), interstitial nephritis ($n = 1$), reflux nephropathy ($n = 2$), obstructive uropathy ($n = 1$) and hypertensive nephrosclerosis ($n = 1$). With the exception of diabetes, patients did not have a history of other illnesses known to cause neuropathy. In total, 15 patients were recruited, receiving thrice-weekly HD using a Polyflux® 201H (surface area 2.1 m^2) dialyzer with a Gambro® 200S dialysis machine (Gambro, Hechingen, Germany). Each dialysis session lasted between 4 and 6 h. The HD machines dialyzed against pure water and Gambro® Select Bag AX250G dialysis concentrate containing sodium (Na+) 140 mmol/L, bicarbonate 34 mmol/L, potassium (K^+) 2.0 mmol/L, calcium 1.5 mmol/L, magnesium 0.50 mmol/L and glucose 1.0 g/L. All patients were adequately dialyzed as verified by the urea reduction ratio (URR > 65%) and equilibrated Kt/V (>1.2) (Daugirdas et al., 1997; Eknoyan et al., 2002).

Clinical assessment as well as US and electrophysiologic studies were conducted before the first dialysis session for the week following a 2-day dialysis free period. Changes in hydration across dialysis were measured with three standard parameters: interdialytic weight change and blood pressure; and volume of ultrafiltration. Post-dialysis ultrasound measurements were performed 30 min after completion of HD. Nerve US was performed by the same investigator (AB) for all subjects, while electrophysiological studies were performed by a different investigator (RA). 15 age- and gender-matched controls were selected from a list of volunteers who had previously expressed interest in undertaking research studies.

2.1. Clinical assessment of neuropathy

All patients underwent comprehensive clinical neurological examination prior to dialysis. The presence and severity of neuropathy was assessed using a modified version of the total neuropathy score (TNS) (Cornblath et al., 1999), a validated clinical measure of neuropathy severity (Arnold et al., 2013a, 2013b, 2016). The TNS is a composite score comprising of the following 8 domains: (i) sensory and (ii) motor neuropathic symptoms, (iii) pin prick sensibility, (iv) vibration detection, (v) strength assessment, (vi) deep tendon reflexes and lower limb (vii) sensory and (viii) motor nerve conduction studies. Each domain is allocated a severity score from 0 (normal) to 4 (severely abnormal). The sum of the individual domains gives the TNS ranging from 0 (no neuropathy) to 32 (disabling neuropathy). Serum electrolytes, urea, creatinine, calcium, magnesium, phosphate, parathyroid hormone and β-2 microglobulin and eGFR (estimated by the Modification of Diet in Renal Disease (*MDRD*) formula) (Levey et al., 1999) were also collected before and after dialysis. Nerve conduction studies (NCS) were undertaken on the tibial, sural, and median nerves using a Medelec Synergy system (Oxford Instruments, Abingdon, United Kingdom), based on standardized protocols (Kimura, 2013). Throughout the study, skin temperature was maintained above 32 °C. The following NCS parameters were recorded; sural nerve sensory nerve action potential (SNAP) amplitude and conduction velocity; tibial nerve compound muscle action potential (CMAP) amplitude and median nerve CMAP amplitude. Our local laboratory reference values were used.

2.2. Ultrasonography

All patients underwent sonographic examination using a MyLabOne system with a 10–18 MHz linear probe (Esaote, Italy). Serial measurements of median nerve cross-sectional area were performed before and after dialysis at a non-entrapment site in the non-fistula arm. 'Musculoskeletal' factory preset (acoustic power 100%, line density set at medium, dynamic range set at 14, persistence set at 1) was used throughout the study. All machine settings, such as depth, gain and focus were also kept constant during each measurement.

All patients were evaluated while sitting comfortably, with the forearm fully supinated and supported by an arm-rest, the elbow flexed to 80–90° and fingers semi-extended. The median nerve was first identified in the carpal tunnel inlet at the level of the pisiform bone. The nerve was then traced proximally, as it runs