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ScienceDirect

Neuromuscular Disorders 27 (2017) 50–56

www.elsevier.com/locate/nmd

Pilot phenotype and natural history study of hereditary neuropathies caused by mutations in the *HSPB1* gene

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Received 21 May 2016; received in revised form 17 September 2016; accepted 2 October 2016

Abstract

Mutations in *HSPB1* are one of the commonest causes of distal Hereditary Motor Neuropathy (dHMN). Transgenic mouse models of the disease have identified HDAC6 inhibitors as promising treatments for the condition paving the way for human trials. A detailed phenotype and natural history study of *HSPB1* neuropathy is therefore required in order to inform the duration and outcome measures of any future trials. Clinical and neurophysiological data and lower limb muscle MRI were collected both prospectively and retrospectively from patients with mutations in *HSPB1*. The natural history was assessed by recording the weighted Charcot–Marie–Tooth Examination Score (CMTES) at annual intervals in a subset of patients. 20 patients from 14 families were recruited into the study. The average age of onset was in the 4th decade. Patients presented with a length dependent neuropathy but with early ankle plantar flexion weakness. Neurophysiology confirmed a motor neuropathy but also showed sensory nerve involvement in most patients. Cross sectional muscle MRI revealed soleus and medial gastrocnemius fat infiltration as an early signature of mutant *HSPB1* disease. In this study neither semi quantitative muscle MRI, the CMTES nor neurophysiology were able to detect disease progression in HSPB1 neuropathy over 1 or 2 years. Further studies are therefore required to identify a suitable biomarker before clinical trials in HSPB1 neuropathy can be undertaken.

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Keywords: Distal hereditary motor neuropathy; Charcot–Marie–Tooth disease; HSPB1; Neuromuscular disease; Peripheral neuropathy

1. Introduction

Charcot–Marie–Tooth disease (CMT) is the most common genetic neuromuscular disease with a population prevalence of 1 in 2500. The distal hereditary motor (dHMN) and hereditary sensory neuropathies refer to forms of CMT in which the disease burden falls on either motor or sensory nerves respectively [1]. CMT and related disorders are a common and genetically heterogenous group of diseases for which more than 80 causative genes have now been described [2]. Mutations in the small heat shock protein, *HSPB1*, although very rare, are the commonest cause of dHMN and have also been reported to cause CMT2 [3,4]. In this study we aimed to characterise the phenotype and natural history of a large, single centre cohort of patients with mutations in *HSPB1*.

HSPB1 is a member of the family of small heat shock proteins. Heat shock proteins (HSPs) are molecular chaperones that are classified according to their molecular weight. HSPs were originally identified as proteins that were induced following heat shock and prevented or reversed the misfolding of cellular proteins [5]. Why mutations in such a ubiquitously expressed protein should result in an isolated neuropathy is not clear.

Mutations in *HSPB1* were first identified as a cause of autosomal dominant dHMN and CMT2 in 2004 [6] following which mutations have been described spanning all regions of the protein [7]. Four mutant *HSPB1* transgenic mouse models of dHMN have now been developed [8–10] and in 2011, d'Ydewalle et al. observed that treatment with a selective HDAC6 inhibitor successfully reversed the clinical phenotype

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http://dx.doi.org/10.1016/j.nmd.2016.10.001

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of both S135F and P182L transgenic mice [8]. Further studies involving the use of HDAC 6 inhibitors in other models of inherited and chemotherapy induced neuropathy have revealed promising pilot results [11,12] paving the way for future clinical trials in patients. Trials of novel therapies in rare diseases, however, require data on the detailed phenotype and natural history of the disease with which to inform appropriate trial design. In this paper we summarise the clinical, neurophysiological and radiological phenotype of a large, single centre cohort of 20 patients from 14 families with mutations in *HSPB1* followed up over a range of 1–10 years by the same investigator (MMR).

2. Methods

Patients were recruited from the inherited neuropathy clinic at the National Hospital for Neurology and Neurosurgery, London. This study was approved by The National Hospital for Neurology and Neurosurgery (NHNN) Research Ethics Committee/Central London REC 3 09/H0716/61.

The *HSPB1* mutations were identified by either Sanger sequencing, whole exome sequencing (WES) or the use of CMT2 disease specific next generation sequencing panels.

2.1. Clinical assessment

Neurological history, examination, and nerve conduction study were performed in all patients. In a subset of patients (patients 1 (ii), 8, 11, 12, 13 (i), 13 (ii), 13 (iv), 14 (ii)), the Rasch modified CMT examination score (hereto referred to as the weighted CMTES) was measured prospectively [13]. As nerve conduction studies were not always performed at the same time as the clinical examination, only the weighted CMTES rather than the Rasch modified CMTNSv2 was calculated. Patients were evaluated annually when possible.

2.2. Lower limb muscle MRI

Six out of 20 patients were scanned at 3 Tesla (Siemens TIM Trio, Erlangen, Germany) in a supine position with surface array coils to receive the signal from the thighs and calves of both limbs. Patients were scanned with a clinical imaging protocol comprising T1 weighted axial imaging and axial STIR imaging as previously described [14]. Muscle MRI scans were assessed for normal and abnormal muscle bulk and for normal and abnormal signal intensity within the different muscle groups. All muscle MRI scans were assessed by an independent observer (JM) and scored according to the 2002 Mercuri classification [15]; a six-point semi-quantitative scale with 0 = normal muscle, 4 = muscle completely replaced by fat. The following muscles were scored bilaterally: rectus femoris, vastus intermedius, vastus lateralis, vastus medialis, semimembranosus, semitendinosus, biceps femoris, adductor magnus, gracilis and sartorius in the thigh; tibialis anterior, peroneus longus, medial gastrocnemius, lateral gastrocnemius, soleus and tibialis posterior in the calf. The mean Mercuri scores for the calf and thigh were also calculated as an overall measure of disease severity on MRI. Serial MRI scans were obtained for two patients. JM assessed these blinded to the chronological order of these two sets of MRI scans.

2.3. Statistical analysis

All statistical analyses were performed using Microsoft Excel (paired t-test) and SPSS version 14.0 (Spearman's rank coefficient and Chi squared analysis).

3. Results

3.1. Mutation analysis

Sanger sequencing of *HSPB1* identified two previously unreported mutations, S135Y and P182A. The S135Y mutation was identified in a sporadic Somalian patient and is likely to be pathogenic as the S135F mutation (i.e. substitution of the same amino acid) is the commonest published pathogenic mutation in HSPB1 [6,7]. DNA was not available from the patient's siblings or parents.

The P182A mutation is likely to be pathogenic as it was found to segregate with the disease in all six family members for whom DNA was available (five affected and one unaffected). In addition, two different missense mutations at the same amino acid (182) have previously been reported to cause dHMN [6,16].

The P182A mutation in family 14 was initially missed by Sanger sequencing of the *HSPB1* gene in two affected family members and subsequently identified using whole exome sequencing. The reason for this false negative result was identified as being due to a 4-bp insertion in intron 2 on the same allele as the P182A mutation (*HSPB1* comprises 3 exons with the P182A mutation residing in exon 3). The 4-bp insertion (GGTG) occurs within a G/C rich region, 3xGGTG repeat sequence, and is present on dbSNP (rs30617181). The additional GGTG repeat prevented this allele from being amplified in the original PCR causing the sequencing to appear normal. Use of a proof reading polymerase confirmed the P182A mutation identified using WES as well as insertion of the GGTG intronic sequence.

3.2. Clinical presentation

The average age of onset of the disease was in the 4th decade although this ranged from the second to the 6th decade (see Table 1.) There was no clear genotype–phenotype correlation; the age of onset was in the second decade for families with both the S135Y and P182A mutations i.e. both within and outside of the alpha crystallin domain (See Fig. 1). Within members of the same family the age of onset was often similar.

Prominent ankle plantar flexion weakness was a common clinical feature unlike most other forms of CMT (see Table 2). Nevertheless, whilst in 8 out of 19 patients, ankle plantar flexion was as-weak as ankle dorsiflexion, in 10 patients, ankle dorsiflexion was weaker than ankle plantar flexion and in only one patient was ankle plantarflexion weaker than dorsiflexion.

The pattern of lower limb weakness was symmetrical in the majority (18/20) of patients. Proximal lower limb weakness was present in 8 out of 20 patients although the neuropathy followed a length dependent pattern in all patients. Reflexes were usually

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