Auditory function in children with Charcot–Marie–Tooth disease

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The peripheral manifestations of the inherited neuropathies are increasingly well characterized, but their effects upon cranial nerve function are not well understood. Hearing loss is recognized in a minority of children with this condition, but has not previously been systemically studied. A clear understanding of the prevalence and degree of auditory difficulties in this population is important as hearing impairment can impact upon speech/language development, social interaction ability and educational progress. The aim of this study was to investigate auditory pathway function, speech perception ability and everyday listening and communication in a group of school-aged children with inherited neuropathies. Twenty-six children with Charcot–Marie–Tooth disease confirmed by genetic testing and physical examination participated. Eighteen had demyelinating neuropathies (Charcot–Marie–Tooth type 1) and eight had the axonal form (Charcot–Marie–Tooth type 2). While each subject had normal or near-normal sound detection, individuals in both disease groups showed electrophysiological evidence of auditory neuropathy with delayed or low amplitude auditory brainstem responses. Auditory perception was also affected, with 40% of subjects with Charcot–Marie–Tooth type 1 and 85% of Charcot–Marie–Tooth type 2 suffering impaired processing of auditory temporal (timing) cues and/or abnormal speech understanding in everyday listening conditions.

Keywords: auditory neuropathy; demyelination; axonopathy; temporal processing; speech perception
Abbreviations: ABR = auditory brainstem response; CMT1–4 = Charcot–Marie–Tooth disease type 1–4; CNC = consonant-nucleus-consonant

Introduction

This study sought to investigate auditory neural dysfunction in a group of school-aged children with Charcot–Marie–Tooth disease (CMT). CMT affects ∼1 in 3000 children (Skre, 1974) and generally presents with symptoms reflecting peripheral nerve dysfunction such as weakness, muscle atrophy, orthopaedic abnormalities and (less commonly) sensory deficits. CMT is subdivided into demyelinating forms (dominantly inherited type 1 (CMT1) and recessively inherited type 4 (CMT4)); generally dominantly inherited axonal type 2 (CMT2)); and intermediate forms, including those inherited in an X-linked fashion. CMT1 is the most common of these (Houlden and Reilly, 2006). On nerve conduction studies, patients with CMT1 and CMT4 have a median nerve motor
conduction velocity of $<38 \text{ m/s}$, while CMT2 is associated with normal conduction velocities ($>38 \text{ m/s}$). In families with intermediate CMT, variable conduction speeds are seen, such that affected individuals in the same family can have motor conduction velocities in both the CMT1 and CMT2 ranges (i.e. above and below 38 m/s).

Hearing loss, that is, impaired detection of sound, is a relatively common phenotypic variant in CMT, and has been reported in both CMT1 (Starr et al., 1996; Kovach et al., 2002) and CMT2 (Satya-Murti et al., 1979; Starr et al., 1996, 2003; Butinar et al., 2008). Most reported cases have shown progressive hearing deficits that have become obvious in adolescence/early adulthood, with only isolated examples showing impaired sound detection in infancy (Hamiel et al., 1993) or early childhood (De Weerdt and Heerspink 1974; Starr et al., 1996).

Auditory deficits associated with CMT reflect neural conduction abnormalities in the afferent auditory pathway (auditory neuropathy). Individuals with auditory neuropathy typically show absent or distorted electrophysiological responses from the VIIIth nerve and auditory brainstem, in conjunction with normal peripheral (cochlear) function (Starr et al., 1996). Auditory nerve involvement in individuals with CMT was first described by Satya-Murti et al. (1979) who found prolongation of waves I–III in scalp-recorded auditory brainstem responses (ABR) from two individuals with dominantly inherited motor-sensory neuropathy and normal peripheral nerve conduction velocities (i.e. presumed CMT2). Subsequent physiological studies involving subjects with both CMT1 (Starr et al., 1996; Kovach et al., 2002) and CMT2 variants (Starr et al., 1996, 2003; Butinar et al., 1999, 2008) have localized the disorder to the auditory nerve, providing evidence of normal cochlear outer hair cell activity (otoacoustic emissions and/or cochlear microphonics) in ears with absent or severely disrupted auditory brainstem potentials. This result pattern is consistent with histopathological examination of the temporal bones of an individual with CMT2 and auditory neuropathy (caused by a missense mutation of the MPZ gene), which revealed selective loss of auditory ganglion cells and nerve fibres in the presence of preserved cochlear hair cells (Starr et al., 2003).

Auditory neuropathy due to demyelinating processes and/or axonopathy is known to affect the neural representation of acoustic signals (Starr et al., 2003). In particular, the resulting disruption of neural synchrony can impair temporal resolution—the ability to perceive rapid changes in auditory signals over time. Psychophysical studies exploring auditory temporal processing have consistently shown impaired detection of brief gaps (silent periods) and rapid envelope variations (sinusoidal amplitude modulation) in continuous stimuli in listeners with auditory neuropathy due to a range of neurodegenerative processes (Zeng et al., 1999, 2005; Rance et al., 2010a, 2012). Auditory temporal resolution has not been widely explored in individuals with CMT, but deficits of both gap detection (Starr et al., 2003; Butinar et al., 2008) and amplitude modulation detection (Starr et al., 2003) have been reported. Furthermore, impaired perception of binaural temporal cues has been demonstrated on Masking-Level Difference tasks, which measure the listener’s capacity to integrate inter-aural signal phase differences (Musiek et al., 1982; Starr et al., 1996).

The primary clinical consequence of auditory temporal processing deficit is disruption of speech understanding. Accurate representation of timing cues is a prerequisite for open-set speech perception. Discrimination of phonemes (individual speech sounds) in running speech, or even in isolated words, requires that the listener perceive the characteristic spectral shapes of individual sounds, and be able to efficiently update this perception to track rapid changes (occurring over the course of only tens of milliseconds) in the flow of speech sounds. Difficulties with speech understanding are common in auditory neuropathy-type hearing loss (Starr et al., 1996; Rance et al., 2004, 2008; Zeng et al., 2005). Perceptual ability can vary—depending on the degree of temporal processing disorder (Zeng et al., 1999; Rance et al., 2004, 2010a)—but most individuals show deficits greater than would be predicted from their behavioural audiogram. Furthermore, severely affected listeners may show no ability to understand speech materials at all despite, in some cases, demonstrating normal or near-normal sound detection.

Speech perception has not been systematically studied in subjects with CMT and auditory neuropathy. Findings in individual cases of both CMT1 (Pareyson et al., 1995; Starr et al., 1996) and CMT2 (Starr et al., 1996, 2003; Butinar et al., 1999, 2008) have, however, shown either negligible speech understanding, or performance levels poorer than expected for ears with peripheral (cochlear) hearing loss.

Impaired speech understanding can have significant detrimental effects upon general communication, and in children, can impair speech and language development, socialization and educational progress (Blamey et al., 2001; Paatsch et al., 2004). To date, no studies have explored the effects of auditory neuropathy in CMT on day-to-day listening, communication or general quality of life. Anecdotal reports in isolated cases have, however, suggested functional deficits. Satya-Murti et al. (1979) indicated that both of their subjects required ‘repeats’ to facilitate conversational understanding. Similarly, Kovach et al. (2002) found that a number of their cohort had poor word recognition in everyday listening circumstances, Fukushima et al. (2011) described a subject with progressive loss of speech understanding in noise and Starr et al. (1996) reported not only that speech perception was a problem, but that it was the earliest and most disabling symptom for their subjects.

This study had three main aims: (i) to investigate auditory neural function in children with CMT1 and CMT2; (ii) to evaluate basic auditory processing in these subjects; and (iii) to determine the functional consequences (upon both formal speech perception and everyday listening ability) of the auditory deficits associated with the disease. These aspects of CMT have not previously been systematically studied in children. Their impact on learning in school-aged children with CMT is unknown, and their nature and severity have not been considered in children with genetically defined inherited neuropathy syndromes.

**Subjects and methods**

This study was approved by the human research ethics committee of the Royal Victorian Eye and Ear Hospital, Melbourne, Australia and
conformed to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants following explanation of the nature, purpose and expected outcomes of the study.

**Subjects**

Twenty-six children (11 females) confirmed by genetic testing to have CMT syndrome were recruited from the Neuromuscular Clinic of the Royal Children’s Hospital (Melbourne). CMT was here defined as a genetically heterogeneous group of disorders characterized by distal limb weakness and wasting, generally in association with hyporeflexia or areflexia, length-dependent sensory loss and skeletal deformities. Eighteen subjects (eight females) had CMT type 1, of which 16 had CMT type 1A caused by a \textit{PMP22} duplication, and two had undefined genotypes with normal sequencing of \textit{MPZ}, i.e. presumed CMT types 1C, 1D or 1E. Eight subjects (three females) had CMT2. Three had mutations in \textit{MFN2} (CMT2A), while five had an axonal neuropathy with negative \textit{MFN2} sequencing. As experimental findings for the subjects with CMT types 1A and 1C, 1D and 1E were similar on each of the auditory measures ($P > 0.05$), results were combined to form the CMT1 subject group. Subject age at assessment ranged from 4 to 19 years. Sound detection ability was either normal or near-normal in all cases (Table 1).

Impairment and disability was assessed in all subjects using either the CMT Neuropathy Score (Shy et al., 2005), or, where neurophysiological data were not available, the clinical component examination score (CMT Examination Score). The CMT Neuropathy Score assesses all facets of the disease, while the CMT Examination Score does not factor in neurophysiological data. Each facet of the assessment (symptoms, signs and neurophysiological changes) is scored on a 0–4 point scale, and subjects are classified as having mild (CMT Neuropathy Score or CMT Examination Score $\leq 10$), moderate (CMT Neuropathy Score $11–20$) or severe deficits (CMT Neuropathy Score $> 20$). These scales have been proven to be reliable and reproducible measures of symptoms, signs and neurophysiological abnormalities in adults with CMT, and correlate well with other measures of disability related to this condition (Shy et al., 2005; Murphy et al., 2011; Pagliano et al., 2011). Although they are less well established in children with genetic

<table>
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<th>Subject</th>
<th>Sex</th>
<th>CMT type</th>
<th>Age at symptom onset (years)</th>
<th>Age at assessment (years)</th>
<th>Median motor NCV (m/s) (lower limit of normal for age)</th>
<th>Median CMAP amplitude (mV) (lower limit of normal for age)</th>
<th>CMTNS/CMTES</th>
<th>AHL (dB)</th>
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<td>15</td>
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<td>1.5</td>
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<td>4.0 (6.7)$^b$</td>
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<td>2.1 (7.7)$^b$</td>
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<td>18</td>
<td>ND</td>
<td>ND</td>
<td>(9)</td>
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<td>0.08 (7.7)$^b$</td>
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<td>3.5 (7.7)$^b$</td>
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</table>

CMT2

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<th>Age at assessment (years)</th>
<th>Median motor NCV (m/s) (lower limit of normal for age)</th>
<th>Median CMAP amplitude (mV) (lower limit of normal for age)</th>
<th>CMTNS/CMTES</th>
<th>AHL (dB)</th>
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<td>Abs</td>
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<td>ND</td>
<td>(1)</td>
<td>12.5</td>
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<td>9.9 (7.7)$^b$</td>
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</table>

Abnormal neural conduction velocities and median motor amplitude values are shown in bold.

a Cruz et al. (1983).
b Parano et al. (1993).

Abs = absent; AHL = average hearing threshold level (dB) based upon sound detection at the 500, 1000, 2000 and 4000 Hz test frequencies; CMAP = median motor amplitude; CMTNS = Charcot–Marie–Tooth disease examination score; CMTES = Charcot–Marie–Tooth disease neuropathy score; NCV = neural conduction velocity; ND = not done.
neuropathies, they are the best validated means of assessment of CMT severity and progression available at this time. All children had mild or moderate deficits as judged using the CMT Neuropathy Score or CMT Examination Score. All remained ambulant but had some deficit related to their neuropathy. Clinical severity was slightly greater than that described in a recent cohort of children with CMT1A (Pagliano et al., 2011), possibly reflecting greater weighting of the CMT Neuropathy Score as opposed to the examination score, which does not include scores pertaining to neurophysiological abnormalities.

Twenty-six control participants matched for age at assessment, gender and 4-frequency average sound detection levels were recruited from the University of Melbourne, School of Audiology Clinic. In each case, the age match was within 12 months of a counterpart with CMT. As such, there was no significant age difference between the CMT groups and their control cohorts (CMT1: 11.7 ± 4.6 years, CMT1 controls: 11.3 ± 4.6 years, P > 0.05; CMT2: 14.5 ± 3.6 years, CMT2 controls: 14.6 ± 3.9 years, P > 0.05). Sound detection thresholds (4-frequency average) were also equivalent between CMT and control groups (CMT1: 14.5 ± 4.5 dB hearing level, CMT1 controls: 12.7 ± 3.5 dB hearing level, P > 0.05; CMT2: 15.9 ± 4.7 dB hearing level, CMT2 controls: 13.7 ± 5.1 dB hearing level, P > 0.05).

Apparatus and procedures

Electrophysiology

ABRs were recorded using a GSI AUDERA evoked potential system. Acoustic click stimuli (100 μs) were presented to each ear individually at 90 dB above normal hearing level. Stimulus presentation rate was 33.1 Hz and EEG samples following 2000 clicks were averaged to produce each test run. Two runs were obtained in each stimulus condition and compared to determine waveform repeatability. Initial assessment in each ear was carried out using rarefaction polarity clicks. In cases where an ABR could not be observed, the testing was repeated using compression polarity stimuli following the procedure described in Rance et al. (1999) to investigate the presence of the cochlear microphonic. Post hoc analysis of the recordings was carried out independently by two experienced clinicians blinded to subject identity. These judges determined the post-stimulus latency of ABR waves I, III and V and the peak-to-peak amplitude of waves I and V.

Auditory temporal processing

Temporal resolution (the ability to perceive rapid changes in auditory signals) was assessed using an amplitude modulation detection task. The psychophysical procedure was as described in Rance et al. (2004, 2010a). Each subject was presented with strings of 500 ms stimuli with 500 ms interstimulus intervals and was trained to respond when they perceived a group of (three) target stimuli randomly inserted into the sequence. A psychometric function was constructed and discrimination threshold in each case was defined as the minimum modulation depth at which the listener could detect the target on 70% of occasions.

The experiment sought the threshold for detection of sinusoidal amplitude modulation occurring at two rates: 10 and 150 Hz. The background stimuli were broadband noise bursts and the modulated (target) stimuli were derived by multiplying the noise burst by a dc-shifted sine wave (Rance et al., 2004). Depth of modulation was determined by the amplitude of the modulating sine wave and stimuli with amplitude modulation depths, defined as 20 μgms, varied from 0 to −30 dB (in 3 dB increments).

Speech perception

Speech perception assessment was carried out for each ear individually. The stimuli were recorded consonant–nucleus–consonant (CNC) words presented to the test ear at 65 dB sound pressure level. A CNC word list, consisting of 50 words, was presented in each of four listening conditions: quiet (no competing signal) and speech in noise presented at 0, +5 and +10 dB signal-to-noise ratios. The competing noise was continuous 4-talker babble. For analysis purposes, the ‘quiet’ condition was assigned a signal-to-noise ratio of +20 dB, reflecting the typical relation between the stimulus and background noise levels in the test environment. Subject responses were phonetically transcribed in real-time and a ‘percentage phonemes correct’ score was generated for each listening condition.

As this experiment required that the subjects imitate the stimulus words, a phonetic profile was obtained for each individual using a modified version of the Royal Children’s Hospital (Melbourne) Articulation Survey. Each subject was able to produce the full range of target phonemes, and as such, errors made during the CNC-word assessment were assumed to reflect hearing (rather than speech production) difficulties.

Hearing disability

Everyday listening and communication ability were investigated using a hearing disability questionnaire (Abbreviated Profile of Hearing Aid Benefit). This 24-question metric explores four aspects of auditory function: communication difficulty, the effect of background noise, the effect of reverberation and aversiveness to loud sounds.

Statistical analyses

The data in this study were analysed using either regression analysis or paired t-tests. As the use of multiple t-tests increases the chance of type 1 error, occasions where the significance value was between P = 0.02 and 0.05 have been highlighted with an asterisk.

Results

Auditory electrophysiology

Charcot–Marie–Tooth disease type 1

Repeatable ABRs were obtained bilaterally for each of the 18 subjects with CMT1 (Fig. 1). Mean response latencies and amplitudes are shown in Table 2. Paired t-tests revealed no difference in ABR wave I latency between the CMT1 and matched control groups (P > 0.05). Significantly prolonged latencies were, however, obtained from CMT1 subjects for wave III (P < 0.001) and wave V (P < 0.005). Neural conduction times (waves I–III and I–V interpeak latencies) were also significantly longer for the CMT1 group (P < 0.001). This finding is reflected in Fig. 2, which shows wave I–V latencies for each of the subjects with CMT. Wave III–V interpeak latency was equivalent for the CMT1 and control groups (P > 0.05).

ABR amplitudes were similar for the CMT1 and matched-control subjects. Mean wave I peak-to-peak amplitude for the CMT1 group was 0.3 ± 0.2 μV and for the controls was 0.3 ± 0.3 μV (P > 0.05). Mean wave V amplitude for the CMT1 subjects was 0.8 ± 0.2 μV and for the controls was 0.7 ± 0.3 μV (P > 0.05). Consequently, the wave V/I amplitude ratio for each group was equivalent (P > 0.05) (Table 2).
Charcot–Marie–Tooth disease type 2

Seven of the eight subjects with CMT2 showed repeatable ABRs. In one individual (Case CMT2 no. 7), potentials were absent in one ear and of poor morphology in the other despite evidence of normal cochlear function (present cochlear microphonic potentials and near-normal sound detection) bilaterally. Response latencies for those CMT2 ears with recordable ABRs \((n = 15)\) were typically normal. Paired \(t\)-tests showed no significant difference between the CMT2 group and matched controls for waves I, III and V \((P > 0.05)\). Similarly, each of the inter-peak latencies \((I–III, III–V\) and \(I–V)\) were equivalent for each group \((P > 0.05)\) although one child (Case CMT2 no. 7) did show mildly prolonged neural conduction in the ear with recordable potentials (Fig. 2).

In contrast, significant ABR amplitude differences were observed for the CMT2 group. While wave I peak-to-peak values were similar \((CMT2: 0.3 ± 0.1 \mu V\); controls: \(0.3 ± 0.2 \mu V\); \(P > 0.05)\), wave V amplitude for the CMT2 cohort was significantly lower \((CMT2: 0.4 ± 0.3 \mu V\); controls: \(0.8 ± 0.3 \mu V\); \(P < 0.05^*\)). This difference is reflected in the waveforms shown in Fig. 1. Wave V/I amplitude ratio was significantly smaller for the CMT2 subjects than controls \((P < 0.05^*\); Table 2).

Group comparison

Multiple regression analysis was used to look for associations between ABR latency and CMT type. As CMT is progressive, subject age at assessment was included as factor, as was subject hearing level, which can influence the outcome of auditory assessment. No relation was found between wave I latency and any of these factors \((P > 0.05)\). In contrast, while absolute latencies for the wave III and V potentials and wave I–V inter-peak latency showed no correlation with sound detection or age, CMT type was a significant factor \((P < 0.05^*\)). That is, auditory neural conduction was significantly slower in children with CMT1 than in those with CMT2 (Table 2).

The relationship between ABR amplitude and CMT type, age at assessment and subject hearing level was also examined. No correlation was found between wave V/I amplitude ratio and either hearing level or age at assessment \((P > 0.05)\), but there was again, a significant group effect \((P < 0.001)\). In this case, the children with CMT2 showed considerably smaller response amplitudes than their counterparts with CMT1 (Table 2).

Table 2 ABR findings (mean ± 1 SD) to rarefaction clicks presented at 90 dB above normal hearing level

<table>
<thead>
<tr>
<th>Group</th>
<th>Latency Wave I (ms)</th>
<th>Latency Wave III (ms)</th>
<th>Latency Wave V (ms)</th>
<th>Inter-peak I–III</th>
<th>Inter-peak III–V</th>
<th>Inter-peak I–V</th>
<th>V/I Amp ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT1</td>
<td>1.4 ± 0.2</td>
<td>3.8 ± 0.3</td>
<td>5.6 ± 0.4</td>
<td>2.4 ± 0.4</td>
<td>1.8 ± 0.2</td>
<td>4.2 ± 0.4</td>
<td>2.8 ± 1.1</td>
</tr>
<tr>
<td>Control (CMT1)</td>
<td>1.4 ± 0.1</td>
<td>3.6 ± 0.1</td>
<td>5.4 ± 0.1</td>
<td>2.2 ± 0.1</td>
<td>1.8 ± 0.1</td>
<td>4.0 ± 0.1</td>
<td>2.5 ± 1.3</td>
</tr>
<tr>
<td>CMT1 versus Control *NS ((P &gt; 0.05))</td>
<td>*NS ((P &gt; 0.001))</td>
<td>*NS ((P &lt; 0.005))</td>
<td>*NS ((P &gt; 0.001))</td>
<td>*NS ((P &gt; 0.001))</td>
<td>*NS ((P &gt; 0.001))</td>
<td>*NS ((P &gt; 0.001))</td>
<td>*NS ((P &gt; 0.05))</td>
</tr>
<tr>
<td>CMT2</td>
<td>1.4 ± 0.1</td>
<td>3.6 ± 0.2</td>
<td>5.5 ± 0.2</td>
<td>2.2 ± 0.2</td>
<td>1.9 ± 0.1</td>
<td>4.0 ± 0.2</td>
<td>1.5 ± 0.7</td>
</tr>
<tr>
<td>Control (CMT2)</td>
<td>1.5 ± 0.1</td>
<td>3.6 ± 0.2</td>
<td>5.5 ± 0.2</td>
<td>2.2 ± 0.2</td>
<td>1.8 ± 0.1</td>
<td>4.0 ± 0.2</td>
<td>2.6 ± 1.7</td>
</tr>
<tr>
<td>CMT2 versus Control *NS ((P &gt; 0.05))</td>
<td>*NS ((P &gt; 0.05))</td>
<td>*NS ((P &gt; 0.05))</td>
<td>*NS ((P &gt; 0.05))</td>
<td>*NS ((P &gt; 0.05))</td>
<td>*NS ((P &gt; 0.05))</td>
<td>*NS ((P &gt; 0.05))</td>
<td>*NS ((P &gt; 0.05))</td>
</tr>
</tbody>
</table>

NS = not significant.
Amplitude modulation detection

**Charcot–Marie–Tooth disease type 1**
Detection of rapid sinusoidal amplitude modulation was poorer for subjects with CMT1 than matched controls. While mean detection thresholds for the low rate (10 Hz modulation frequency) stimulus were equivalent (Table 3), listeners with CMT required significantly larger modulation depths to identify high rate (150 Hz) amplitude changes. Mean detection threshold for the CMT1 group in this case was $\pm 23.1 \pm 2.7$ dB (33.1% of maximum amplitude) compared with $\pm 13.3 \pm 3.8$ dB (15.0% of maximum amplitude) for the matched controls ($P < 0.001$). Figure 3 shows the 150 Hz amplitude modulation detection threshold for each of the CMT1 subjects (ears).

**Charcot–Marie–Tooth disease type 2**
Subjects with CMT2 also showed an impaired ability to detect rapid amplitude variations. Again, while low rate (10 Hz) modulation detection was equivalent to matched controls (Table 3), detection of high rate (150 Hz) modulation was significantly poorer.

Mean detection limen for the CMT2 group in this case was $\pm 9.6 \pm 3.0$ dB (33.1% of maximum amplitude) compared with $\pm 17.4 \pm 1.1$ dB (13.5% of maximum amplitude) for the controls ($P < 0.001$). Results for individual CMT2 subjects (ears) are shown in Fig. 3.

**Group comparison**
Multiple regression analysis was used to look for correlations between amplitude modulation detection ability and CMT type, age at assessment and subject hearing level. No relation was found between low rate (10 Hz) modulation detection and any of these factors ($P > 0.05$). For high rate (150 Hz) detection, there was no association with sound detection or age ($P > 0.05$), but there was a significant group difference ($P < 0.001$) reflecting poorer temporal resolution in the children with CMT2 (Table 3).

### Table 3 Perceptual findings (mean ± 1 SD) for CMT1, CMT2 and their matched control cohorts

<table>
<thead>
<tr>
<th>Group</th>
<th>AM (10 Hz)</th>
<th>AM (150 Hz)</th>
<th>CNC (Quiet)</th>
<th>CNC (+10 dB)</th>
<th>CNC (+5 dB)</th>
<th>CNC (+0 dB)</th>
<th>Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT1</td>
<td>$-23.1 \pm 2.7$</td>
<td>$-13.3 \pm 3.8$</td>
<td>$94.6 \pm 3.0$</td>
<td>$80.5 \pm 7.3$</td>
<td>$68.0 \pm 8.9$</td>
<td>$36.8 \pm 9.9$</td>
<td>$2.7 \pm 0.5$</td>
</tr>
<tr>
<td>Control (CMT1)</td>
<td>$-23.7 \pm 2.6$</td>
<td>$-16.4 \pm 2.2$</td>
<td>$97.6 \pm 1.8$</td>
<td>$88.4 \pm 5.3$</td>
<td>$77.7 \pm 8.0$</td>
<td>$54.1 \pm 6.1$</td>
<td>$2.0 \pm 0.3$</td>
</tr>
<tr>
<td>CMT1 versus Control</td>
<td>NS ($P &gt; 0.05$)</td>
<td>$P &lt; 0.001$</td>
<td>$P &lt; 0.001$</td>
<td>$P &lt; 0.001$</td>
<td>$P &lt; 0.001$</td>
<td>$P &lt; 0.001$</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>CMT2</td>
<td>$-22.7 \pm 2.8$</td>
<td>$-9.6 \pm 3.0$</td>
<td>$93.1 \pm 7.1$</td>
<td>$78.4 \pm 8.4$</td>
<td>$61.1 \pm 10.4$</td>
<td>$30.9 \pm 4.7$</td>
<td>$3.0 \pm 0.3$</td>
</tr>
<tr>
<td>Control (CMT2)</td>
<td>$-24.0 \pm 2.4$</td>
<td>$-17.4 \pm 1.1$</td>
<td>$97.1 \pm 2.3$</td>
<td>$88.2 \pm 5.3$</td>
<td>$78.3 \pm 8.1$</td>
<td>$54.9 \pm 6.3$</td>
<td>$1.9 \pm 0.4$</td>
</tr>
<tr>
<td>CMT2 versus Control</td>
<td>NS ($P &gt; 0.05$)</td>
<td>$P &lt; 0.001$</td>
<td>$P &lt; 0.05$</td>
<td>$P &lt; 0.01$</td>
<td>$P &lt; 0.01$</td>
<td>$P &lt; 0.01$</td>
<td>$P &lt; 0.001$</td>
</tr>
</tbody>
</table>

Amplitude modulation detection is the smallest detectable modulation depth (dB) in a burst of white noise and CNC score is the percentage of phonemes (individual speech sounds) correctly discriminated by the listener. AM = amplitude modulation; NS = not significant.

**Speech perception**

**Charcot–Marie–Tooth disease type 1**
Speech perception was significantly impaired in children with CMT1. Mean CNC phoneme scores were lower than those of the matched control cohort for listening in quiet ($P < 0.001$) and for each of the speech-in-noise conditions ($P < 0.001$) (Table 3). Group differences were most pronounced in the most challenging listening condition (0 dB signal-to-noise ratio) where children with CMT1 typically discriminated about one-third fewer speech sounds than their control counterparts. This performance difference is reflected in Fig. 4, which shows the speech perception score for each child with CMT1. Furthermore, regression slopes (calculated for each subject) to describe the change in CNC-phoneme score with decreasing signal-to-noise ratio revealed significantly steeper performance decline in the children with CMT1 in the presence of background noise ($P < 0.001$) (Table 3).

**Charcot–Marie–Tooth disease type 2**
Participants with CMT2 also showed poorer speech perception scores than matched controls. Significant differences in CNC score were obtained for each listening condition, and again, deficits in the CMT2 listeners were most pronounced when the target stimuli were presented with a competing noise (Table 3). Individual results for CMT2 subjects are shown in Fig. 4. The exaggerated effect of background noise on perception was also reflected in the within-subject performance functions, which
showed significantly steeper regression slopes in the children with CMT2.

**Group comparison**

Speech perception ability was affected to an equivalent degree in children with CMT1 and CMT2. Multiple regression found no relation between CNC score (both in quiet and in noise) and CMT type, age at assessment and subject hearing level ($P > 0.05$).

**Hearing disability**

**Charcot–Marie–Tooth disease type 1**

Children with CMT1 reported a higher degree of everyday listening and communication difficulty than the controls. Abbreviated Profile of Hearing Aid Benefit questionnaire scores (reflecting the proportion of circumstances in which they perceived a problem) were significantly higher for the ease of communication ($P < 0.001$), effect of background noise ($P < 0.005$) and effect of reverberation ($P < 0.005$) subcategories and for the Global Score generated from these subscores ($P < 0.001$) (Table 4).

**Charcot–Marie–Tooth disease type 2**

Subjects with CMT2 also reported a greater degree of hearing-related problems than their peers. Mean Abbreviated Profile of Hearing Aid Benefit scores for the ease of communication, background noise and reverberation subcategories and for the Global Score were all higher than for the controls ($P < 0.05^*$). Sound aversion was similar in the CMT2 and control cohorts ($P > 0.05$).

**Group comparison**

Degree of self-reported hearing disability was similar in children with CMT1 and CMT2. Multiple regression analysis found no relation between any of the Abbreviated Profile of Hearing Aid Benefit subcategory scores and CMT type, age at assessment and subject hearing level ($P > 0.05$).

**Relations between auditory measures**

Pearson $r$ analyses were carried out to investigate relations between auditory neural conduction time [ABR (wave I–V latency), ABR amplitude (ABR V/I ratio), temporal processing (amplitude modulation (150 Hz) detection threshold)] speech perception in noise (0 dB signal-to-noise ratio) and hearing disability ratings (Abbreviated Profile of Hearing Aid Benefit Global score). Findings for both CMT groups are shown in Table 5. For children with CMT1, ABR inter-peak latency was highly correlated with each of the other auditory measures ($P < 0.001$). That is, those children with the most disordered auditory neural conduction were also those with the most impaired temporal processing, poorest speech understanding and greatest degree of everyday listening impairment. ABR amplitude (which was typically normal in this group) was not correlated with any of the other auditory measures ($P > 0.05$).

For children with CMT2, no significant correlations between auditory measures were found. As discussed previously, ABR amplitudes were reduced in individuals with this form of the disease, but the degree of amplitude reduction (wave V/I ratio) was not correlated with the perceptual findings. This result may reflect the small subject number in the CMT2 group ($n = 8$).

**Table 4** Abbreviated Profile of Hearing Aid Benefit Hearing Disability questionnaire findings for CMT1, CMT2 and their matched control cohorts

<table>
<thead>
<tr>
<th>Group</th>
<th>Ease of communication</th>
<th>Background noise</th>
<th>Reverberation</th>
<th>Aversiveness</th>
<th>Global Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT1</td>
<td>10.7 ± 5.6</td>
<td>26.3 ± 11.2</td>
<td>13.0 ± 7.0</td>
<td>13.6 ± 13.1</td>
<td>16.7 ± 6.7</td>
</tr>
<tr>
<td>Control (CMT1)</td>
<td>3.2 ± 1.8</td>
<td>14.6 ± 8.3</td>
<td>6.5 ± 3.5</td>
<td>16.4 ± 9.6</td>
<td>8.4 ± 4.4</td>
</tr>
<tr>
<td>CMT1 versus Control</td>
<td>$P &lt; 0.001$</td>
<td>$P &lt; 0.005$</td>
<td>$P &lt; 0.005$</td>
<td>NS $P &gt; 0.05$</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>CMT2</td>
<td>11.8 ± 7.5</td>
<td>19.5 ± 7.9</td>
<td>19.2 ± 10.5</td>
<td>14.3 ± 17.2</td>
<td>16.3 ± 8.0</td>
</tr>
<tr>
<td>Control (CMT2)</td>
<td>3.2 ± 2.1</td>
<td>9.7 ± 3.6</td>
<td>5.3 ± 2.0</td>
<td>15.8 ± 20.3</td>
<td>7.3 ± 3.5</td>
</tr>
<tr>
<td>CMT2 versus Control</td>
<td>$P &lt; 0.02$</td>
<td>$P &lt; 0.01$</td>
<td>$P &lt; 0.01$</td>
<td>NS $P &gt; 0.05$</td>
<td>$P &lt; 0.05^*$</td>
</tr>
</tbody>
</table>

Values represent the percentage of everyday listening situations in which the child perceived a difficulty (mean ± 1 SD). NS = not significant.
Relations between auditory and non-auditory measures

In subjects with CMT1, correlation analyses showed no significant relation between age of symptom onset and disease duration and any of the auditory measures (Table 6). Both measures of peripheral nerve function (neural conduction velocity and median motor amplitude) were negatively correlated with ABR latency and hearing disability estimates. Furthermore, the CMT Neuropathy Score correlated highly with each of the auditory measures ($P < 0.02$). This relation was particularly clear for ABR latency. As can be seen in Fig. 5, six of the seven individuals with prolonged neural conduction (ABR I–V latency > 4.3 ms) showed a CMT Neuropathy Score in the moderate deficit range. The seventh subject showed a borderline result (CMT Neuropathy Score = 10).

In subjects with CMT2, there were no correlations between any of the auditory and non-auditory measures (although this result may be a reflection of the relatively small sample size).

**Discussion**

The children with CMT in this study all demonstrated normal or near-normal sound detection, but in many cases showed abnormal auditory nerve function and auditory processing deficits consistent
with impaired representation of timing cues in the central auditory pathways.

The auditory-evoked potential findings in this study were consistent with the pathophysiological mechanisms underlying CMT. In children with CMT1, ABR amplitudes were normal, but absolute peak latencies (waves III and V) were delayed and inter-peak latencies (particularly between waves I and III) were prolonged relative to matched controls. This pattern is in keeping with the demyelination characteristic of CMT1, which is characterized by reduced conduction velocities with relative preservation of axon numbers (Dyck and Lambert, 1968). Central conduction in the auditory brainstem has previously been suggested to be normal in persons with CMT type 1A (Nicholson and Corbett, 1996; Neijenhuis, 2003). Other studies have, however, found increased ABR conduction times similar to those identified in our cohort (Neijenhuis, 2003). Other studies have, however, found increased auditory brainstem has previously been suggested to be normal numbers (Dyck and Lambert, 1968). Central conduction in the present study, neural conduction speed in the auditory pathways (ABR I–V latency) correlated well with peripheral nerve conduction velocities.

In contrast, ABRs in children with CMT2 typically showed normal latency, but reduced (wave V) peak-to-peak amplitude. This pattern is consistent with axonopathy, which in CMT2 is characterized by fibre loss with relative preservation of neural conduction velocity (Dyck and Lambert, 1968). Similar ABR findings have been reported in individuals with Friedreich ataxia, another neurodegenerative disease in which auditory neuropathy occurs as a consequence of peripheral nerve axonopathy (Spoendlin, 1974; Rance et al., 2008). One child in our series (Case CMT2 no. 7) did show both prolonged ABR (I–V) latency and reduced response amplitude, perhaps reflecting the fact the axonal survival and demyelinating processes are not entirely independent.

Basic auditory processing was disrupted in children with CMT. While amplitude modulation detection for a low rate (10Hz modulation frequency) stimulus was normal in both CMT1 and CMT2 cohorts [suggesting normal sensitivity to amplitude (level) changes], both groups showed an impaired capacity to detect modulation occurring at a rapid rate (150Hz modulation frequency). That is, their auditory pathways were less able to encode signal changes occurring over a brief (6–7 ms) time course. The precise mechanisms underlying this temporal processing deficit are not fully understood, but both demyelinating and axonal pathologies are known to result in disruption of the synchrony of neural firing (Starr et al., 1996, 2003) which could, in turn, produce a time-smeared neural representation of acoustic stimuli. In the case of demyelinating neuropathy, desynchrony occurs when disruption of the neural insulator results in slowed/inconsistent conduction of neural inputs and/or a reduced ability to transmit trains of pulses (Brown and Watson, 2002). Axonopathy may also produce desynchrony where inconsistent conduction velocities result from partially damaged (but still functioning) fibres, secondary demyelination and/or conduction block (Brown and Watson, 2002). Auditory temporal processing deficits have not been widely explored in CMT populations (Starr et al., 2003; Butinar et al., 2008) but are a cardinal feature of auditory neuropathy due to both demyelinating and axonal mechanisms (Starr et al., 1996; Rance et al., 2004, 2008, 2011; Zeng et al., 2005).

A high proportion of the subjects in this study (61% of the CMT1 and 87% of the CMT2 cohorts) showed significantly impaired speech perception ability in test conditions designed to replicate everyday communication circumstances. As these children all enjoyed normal or near-normal sound detection, distortion (at the neural level) of the speech signal, rather than audiability, is likely to have been the limiting factor. Distortion of complex signals (such as speech) can take a number of forms. Peripheral (cochlear) hearing loss, for example, in addition to making sounds softer or more difficult to detect, can impair the processing of frequency cues making pitch differences less salient (Moore and Peters, 1992). Signal distortion due to auditory neuropathy can also affect frequency discrimination (to a limited extent), but primarily affects the neural representation of temporal information (Rance et al., 2004, 2010; Zeng et al., 2005). In speech for example, perception of subtle timing cues such as voice onset times (which allow differentiation between voiced and unvoiced consonants) is specifically affected in auditory neuropathy listeners with temporal processing disorder (Rance et al., 2008, 2010a). The characteristics of the signal distortion affecting children with CMT in this study have not been determined, but are likely to be due to temporal processing as speech perception ability (in the CMT1 cohort at least) was significantly correlated with amplitude modulation detection threshold.

Speech perception deficits were observed in all conditions, but were particularly pronounced when the speech signals were presented in the presence of background noise. Performance gradients describing the decline in perceptual ability with increasing noise level were calculated for each individual and were consistently steeper in the CMT cohorts than matched controls, indicating that children with CMT were more affected by the competing signal. Group differences were most pronounced in the 0dB signal-to-noise condition (where speech and noise were presented
at the same level). In this case, children in both CMT groups were only able to correctly imitate one in every three phonemes (i.e. only one speech sound per word) on the CNC discrimination test, where their normal peers could identify more than half of the phonemes. This reduced ability to cope with competing signals represents a significant communication and educational challenge, as the signal-to-noise ratio in a typical classroom is only $\sim 0\text{--}3\text{~dB}$ (Crandell and Smaldino, 2000).

Problems with listening in noise have not been previously described in individuals with CMT but are a consistent feature of auditory neuropathy-type hearing loss (Starr et al., 1996; Rance et al., 2008, 2011). The mechanisms underlying speech-in-noise problems are unclear, but there is strong psychophysical evidence indicating that perception of basic auditory signals (such as pure tones) is more affected by simultaneous masking noise in listeners with auditory neuropathy than controls (Kraus et al., 2000; Zeng et al., 2005). Furthermore, forward and backward masking studies (exploring the degree to which detection of a brief signal is affected by sounds occurring before and after the target) have also shown excessive effects in listeners with temporal processing disorder due to auditory neuropathy (Kraus et al., 2000; Zeng et al., 2005). As such, it appears that individuals with auditory neuropathy are less able to separate sounds occurring both simultaneously and successively. In natural listening conditions where background noise levels fluctuate continuously, this may mean that individuals with auditory neuropathy are less able to use brief quiet periods to access the speech signal.

The auditory deficits demonstrated in the various ‘laboratory-based’ assessments were also reflected in self-reported hearing disability ratings. Where control subjects considered that they had hearing and communication difficulties in $<10\%$ of everyday situations, children in both CMT1 and CMT2 groups felt that they struggled in approximately twice as many circumstances and reported particular difficulty understanding conversational speech in the presence of background noise.

**Summary and recommendations**

The speech perception and hearing disability findings in this study have revealed functional deficits sufficient to impact on day-to-day communication in a relatively high proportion of children in a school-aged CMT cohort. These perceptual limitations are similar in nature and degree for both CMT1 and CMT2 forms of the disease despite the fact that they involve disparate underlying mechanisms. The data suggest that auditory evaluation should be part of the management regime for every individual with CMT1 and CMT2 and should include auditory evoked potential and speech perception (in noise) assessment. Standard audiometry is clearly inadequate for this population, as sound detection can be normal in listeners with severe auditory processing disorder.

Management of auditory neuropathy is problematic, as signal distortion rather than audibility is the primary issue. Conventional hearing aids, for example whose primary function is to make sounds louder, tend to be ineffective in such cases. The use of listening tactics (such as seating an affected student near the front of the class) may be helpful in maximizing the amount information available. Recent experience has also suggested that personal FM-listening devices (which involve radio wave transmission of speech signals from a speaker wearing a transmitter to the listener wearing a receiver) may also be useful in improving everyday communication for individuals with auditory neuropathy (Rance et al., 2010b).

Auditory neural function may worsen with disease progression. Loss of ABRs over time has been reported in adults (Starr et al., 2003; Seeman et al., 2004), which may correlate with the slow axonal degeneration apparent in adults with CMT types 1 and 2 (Roy et al., 1989; Krajewski et al., 2000). Also unknown is the age at which auditory neuropathy manifests in small children with CMT, and the extent to which this correlates with the maturational changes seen in children with inherited neuropathies (Yiu et al., 2008).

The findings of this study suggest that measures of auditory function may be useful in tracking disease progression in individuals with CMT. There is a lack of longitudinal data (particularly in affected children) although evidence of ABR deterioration over time has been reported in a few adults with CMT (Starr et al., 2003; Seeman et al., 2004). A focus of further studies will be serial investigations in children with abnormal ABRs. The cross-sectional data provided in this study does, however, suggest a correlation between auditory function and overall disease progress. Group data (for the CMT1 cohort at least) showed strong correlations between each of our auditory measures and overall level of disability, as quantified by the CMT neuropathy scale. This was particularly the case for the neural conduction findings which suggested that an abnormal result (ABR I–V latency $>4.3\text{~ms}$) can broadly predict a child’s overall level of dysfunction. Further studies will assess these findings in the light of more specific and sensitive measures of disease severity in paediatric CMT, and will evaluate whether auditory measures may represent a potential biomarker for disease progression and response to treatment in interventional studies.

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