Auditory neuropathy in a patient with hemochromatosis

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Abstract

Objective: To evaluate the auditory function of an individual with genetically confirmed hemochromatosis.

Methods: A 57 year old male with mildly impaired sound detection thresholds underwent a range of behavioural, electroacoustic and electrophysiologic assessments. These included the recording of otoacoustic emissions and auditory brainstem responses, measurement of monaural temporal resolution and evaluation of binaural speech processing. Findings for this patient were subsequently compared with those of 80 healthy controls with similar audiometric thresholds.

Results: The patient showed the three cardinal features of auditory neuropathy, presenting with evidence of normal cochlear outer hair cell function, disrupted neural activity in the auditory nerve/brainstem and impaired temporal processing. His functional hearing ability (speech perception) was significantly affected and suggested a reduced capacity to use localization cues to segregate signals in the presence of background noise.

Conclusion: We present the first case of an individual with hemochromatosis and auditory neuropathy. The findings for this patient highlight the need for careful evaluation of auditory function in individuals with the disorder.

1. Introduction

Hemochromatosis is a hereditary disorder characterized by excessive absorption and storage of iron from the diet. Excess iron is deposited in various organs including the skin (causing bronze pigmentation), the heart (causing arrhythmia), the testes (causing loss of libido) and the pancreas (causing diabetes) (Neumann, 1948). Primary hemochromatosis is typically caused by a mutation of the HFE gene located on chromosome 6p21.3. Symptom manifestation is modified by several environmental factors (including dietary iron intake and alcohol consumption) and is 5−10 times more common in men than women. Symptoms appear between the ages of 40 and 60 years in approximately 70% of individuals (Neumann, 1948).

The effects of excessive iron on the auditory system are yet to be fully explored, but there is some evidence that both chronic and acute iron deposition can impair function. Superficial siderosis is a disorder of the central nervous system in which repeated haemorrhaging into the subarachnoid space leads to accumulation of hemosiderin (iron oxide) deposits in neuronal tissues close to the cerebrospinal fluid (Gao et al., 2015). The most susceptible cells are those in the cerebellum and auditory pathway and both intracochlear damage and VIIIth nerve demyelination/axonopathy have been

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reported (Tomlinson and Walton, 1964; Kale et al., 2003; Sydlowski et al., 2009). As a result, progressive hearing impairment is a cardinal feature of the disease (Koeppen and Dentinger, 1988; Fearnley et al., 1995; Kobayashi et al., 2004). Furthermore, sudden hearing loss has recently been associated with mutations in genotypes such as FPN1−8 GG which is thought to control iron homeostasis in the inner ear (Castiglione et al., 2015).

The primary neurologic signs of hemochromatosis are progressive ataxia, gait disturbance and hearing loss (Neumann, 1948). Progressive hearing deficit (as measured by impaired sound detection thresholds) has been reported in patients with the disease (Lewey and Govons 1942; Neumann, 1948) but the underlying mechanisms and functional consequences have not been fully considered. In this study we compare peripheral auditory function, auditory processing and binaural speech perception findings for an individual with hemochromatosis with those obtained from a of group healthy matched controls.

2. Materials 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 following explanation of the project's nature, purpose and expected outcomes.

2.1. Participants

Patient DM was recruited through the Medical Retina Clinic at the Royal Victorian Eye and Ear Hospital as part of a broader study investigating auditory function in individuals with Type 1 diabetes (T1DM). He was aged 57 years at assessment and had been diagnosed with hemochromatosis at aged 47 years following genetic testing which indicated a C282Y mutation of the *HFE* gene. His clinical presentation included liver failure, hypertension, hypogonadism, Charcot's (neuropathic) anthropathy and diabetes due to pancreatic disease. The patient's diabetes was managed via a daily subcutaneous insulin regimen and at the time of assessment his glycated haemoglobin levels (HBA1c) were mildly elevated (8.8%). Neurological history and physical examination showed evidence of distal symmetrical polyneuropathy with abnormal responses across a range of sensory modalities (Michigan Neuropathy Screening Instrument [MNSI] rating: 2). His visual acuity was significantly impaired (LogMAR: 0.8) with evidence of proliferative diabetic retinopathy (Airlie House Classification System: 4) and macular oedema (Airlie House Classification System: 2). Audiometric thresholds were mildly elevated, with both ears showing 4-frequency average hearing levels of 26.25 dBHL (Fig. 1A). Despite these impaired sound detection levels, robust Distortion Product Otoacoustic Emission (DPOAE) responses were observed bilaterally (Fig. 1B and C).

Auditory findings for Patient DM were compared with data from 80 healthy control subjects with sound detection thresholds in the mild hearing loss range (4 frequency average: 24.7 ± 5.2 dBHL). Selected results for these individuals (39 female) have been published previously (Rance et al., 2012a, 2012b; 2014). Age at assessment for the group ranged from 10 years to 76 years (52.2 ± 14.9 years).

2.2. Experimental procedures

Each subject underwent audiometric assessment using ER-4 insert phones and a portable audiometer in a quiet room where background noise levels were less than 40 dBA. Sound detection thresholds were established at octave frequencies across the audiometric range (250 Hz−8 kHz) using standard threshold seeking techniques. A 4-frequency average level based on hearing thresholds at 500-, 1000-, 2000- and 4000 Hz was calculated for each ear.

Auditory brainstem responses (ABRs) were recorded to 100 µs acoustic click stimuli presented to each ear individually at 90 dBnHL. Electroencephalographic samples following 2000 clicks were averaged to produce each test run. Responses were obtained to clicks at presentation rates of 8 Hz, 33 Hz, 57 Hz, 75 Hz and 100 Hz. A minimum of two runs were obtained in each stimulus condition and compared to determine waveform repeatability. The highest rate at which a repeatable ABR could be observed was determined for each ear. Furthermore, post-stimulus latency of ABR waves I, III and V and the wave V/I peak-to-peak amplitude ratio was established for the 8 Hz presentation rate.

Temporal resolution (the ability to perceive changes in auditory signals over time) was assessed using an amplitude modulation (AM) detection task. The psychophysical protocol employed an adaptive, three-alternative, forced-choice procedure to determine the 70.7% correct response criterion. The experiment sought the threshold for detection of sinusoidal AM occurring at two rates: 10 Hz and 150 Hz. The background stimuli were broadband noisebursts and the modulated (target) stimuli were derived by multiplying the noiseburst by a dc-shifted sine wave as per Rance et al. (2004). Depth of modulation was determined by the amplitude of the modulating sine wave and stimuli with AM depths, defined as 20 logm, varied from 0 to −30 dB (in 3 dB increments).

Binaural speech perception assessment was carried out using the Listening in Spatialized Noise (LISN-S) test which measures the subject's ability to segregate a target speech signal from a competing speech noise (Cameron and Dillon, 2007). The test is administered under headphones, but a 3-dimensional auditory environment is created by synthesizing the test stimuli using a head-related transfer function (Cameron and Dillon, 2008). Speech reception threshold (the signal-to-noise ratio required for the listener to identify 50% of the words in target sentences) is established in 4 conditions which vary in terms of the location of the noise source (0° versus 90° azimuth) and vocal quality of the speaker (same or different talker used to produce the target and background signals).
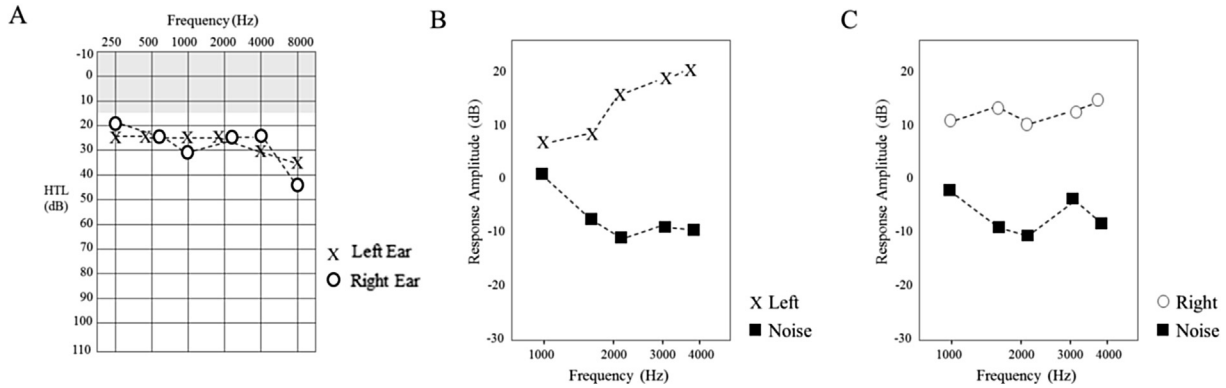
Fig. 1. Behavioural audiogram (Panel A) and Distortion Product Otoacoustic Emission (Panel B and Panel C) results for Patient DM.

3. Results

3.1. Auditory brainstem response

Subject DM showed repeatable ABR waveforms to acoustic click stimuli presented to each ear at the 8 Hz presentation rate. Waveform latencies are shown in Table 1. Absolute peak latencies for wave I and wave V for each ear were within the control group normative range (mean ± 2SD), but wave III latencies were prolonged. Interpeak latencies (III—V) were normal, but wave I—III interpeak times were significantly longer (>mean + 2 SD) than those of the control participants. Response amplitudes (wave V/I ratio) for patient DM were within the control group mean ± 2 SD range (Table 1).

Auditory brainstem potentials for Subject DM were abnormally affected by increases in stimulus presentation rate. Mean maximum rate with a recordable ABR for the control group was 97.9 ± 7.0 Hz. Patient DM, in contrast, only showed an ABR to acoustic clicks presented to the left ear at 8 Hz (Fig. 2A). For the right ear, repeatable responses were observed for presentation rates ≤75 Hz (Fig. 2B), but waveforms to high rate stimuli were significantly delayed relative to controls (Fig. 2C).

3.2. Auditory temporal processing

Identification of rapid sinusoidal amplitude modulation was impaired in Subject DM. While his AM detection thresholds to low rate stimuli (10 Hz) fell within the control group normative range (mean ± 2 SD), his high rate AM thresholds (150 Hz) for stimuli presented to both the left and right ears were significantly higher (worse) than those of the control

cohort (Fig. 3). This pattern is indicative of temporal processing disorder. Normal identification of modulation at 10 Hz suggests unimpaired discrimination of signal level variations. Depressed AM detection at 150 Hz, in contrast, reflects an impaired capacity of the auditory pathway to encode signal changes occurring over a brief time course (Rance et al., 2010).

3.3. Binaural speech perception in noise

Subject DM showed impaired speech perception in background noise for listening conditions in which binaural difference cues were available. For both the DV90 (different voices/target and background speech spatially separated by 90°) and SV90 (same voice/target and background separated by 90°) conditions, his speech reception threshold was poorer than the mean ± 2 SD performance range of the control cohort (Fig. 4). In contrast, his performance for listening conditions in which the target speech and noise were co-located (DV0 and SV0) was within the normal range (Fig. 4).

4. Discussion

The hemochromatosis patient described in this study presented with the 3 cardinal features of the auditory neuropathy (AN) type hearing loss: normal cochlear outer hair cell function (with robust otoacoustic emission responses bilaterally), disrupted neural conduction in the auditory nerve/brainstem and impaired processing of auditory temporal cues.

Repeatable auditory brainstem responses were obtained (to low rate stimuli) in each ear, but absolute peak latencies (wave III) were increased in each ear relative to matched controls. Wave I—III inter-peak latencies were also prolonged

Table 1
ABR findings to 90 dBnHL acoustic click stimuli presented at a rate of 8 Hz.

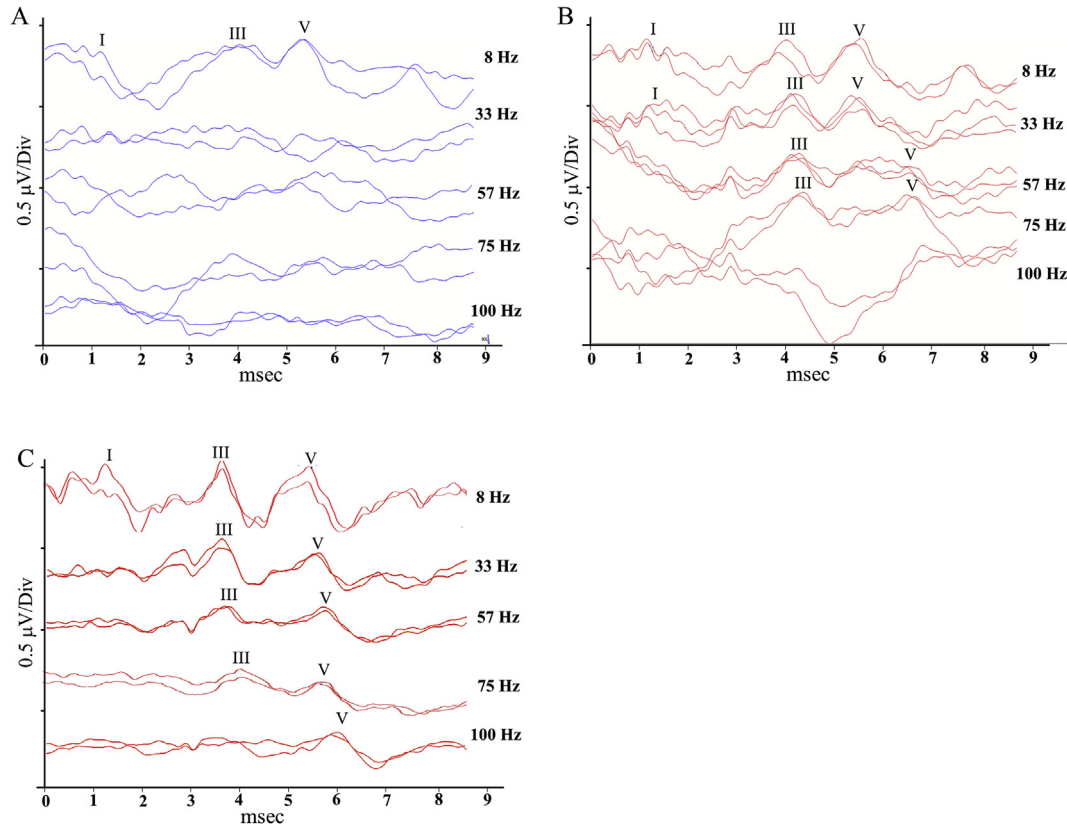|	Waveform latencies (8 Hz)						Amplitude ratio (V/I)	Maximum rate
	I	III	V	I—III	III—V	I—V		
Control group mean (SD)	1.48 (0.14)	3.66 (0.10)	5.54 (0.24)	2.18 (0.14)	1.88 (0.14)	4.05 (0.18)	2.21 (1.44)	97.92 (7.01)
DM (left Ear)	1.32	3.86	5.50	2.54	1.64	4.18	0.90	8.0
DM (right Ear)	1.32	3.90	5.48	2.58	1.58	4.16	1.68	75.0

Fig. 2. Auditory brainstem responses for Subject DM to acoustic click stimuli at presentation rates ranging from 8 Hz to 100 Hz. Findings for stimuli presented to the left ear are shown in Panel A and to the right ear are shown in Panel B. Tracings for a typical control subject are shown in Figure C.
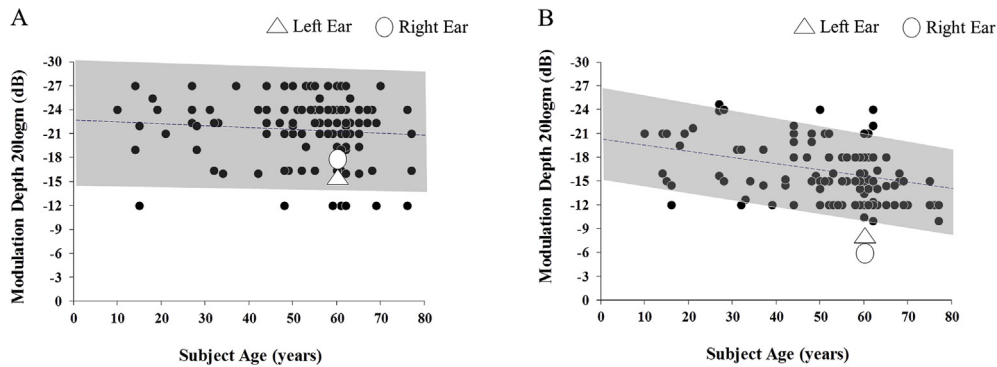

Fig. 3. Amplitude modulation detection thresholds for Subject DM (unfilled data points) and hearing-level matched controls (filled data points). The shaded area represents the mean ± 2 SD range for the control group. Panel A shows findings for stimuli modulated at a rate of 10 Hz. Panel B shows findings for amplitude modulation at a rate of 150 Hz.

bilaterally indicating reduced conduction velocity between the distal portion of the auditory nerve and the cochlear nucleus. The mechanism(s) underlying this result pattern is unclear, but post-mortem histologic investigation in another hemochromatic patient with similar neurologic history (progressive bilateral hearing loss and balance disturbance), revealed evidence of pyknotic degenerative changes in the VIIIth nerve dorsal nucleus (Neumann, 1948).

Abnormal brainstem responses to high rate stimuli were also observed in Patient DM. The effect of stimulus rate on the

ABR in normally-hearing adults is well understood with numerous studies showing consistent latency prolongation and amplitude reduction as presentation rate is increased beyond 20 Hz (Don et al., 1977; Picton et al., 1981; Burkhard et al., 1990). Rate effects in individuals with neuropathology have been less well explored, but abnormal latency shifts and disappearance of later ABR waves have been described for a range of peripheral and CNS pathologies including acoustic neuroma (Daly et al., 1977), hypoxia (Hecox et al., 1981), mixed CNS disease (Pratt et al., 1981; Fowler and Noffsinger,
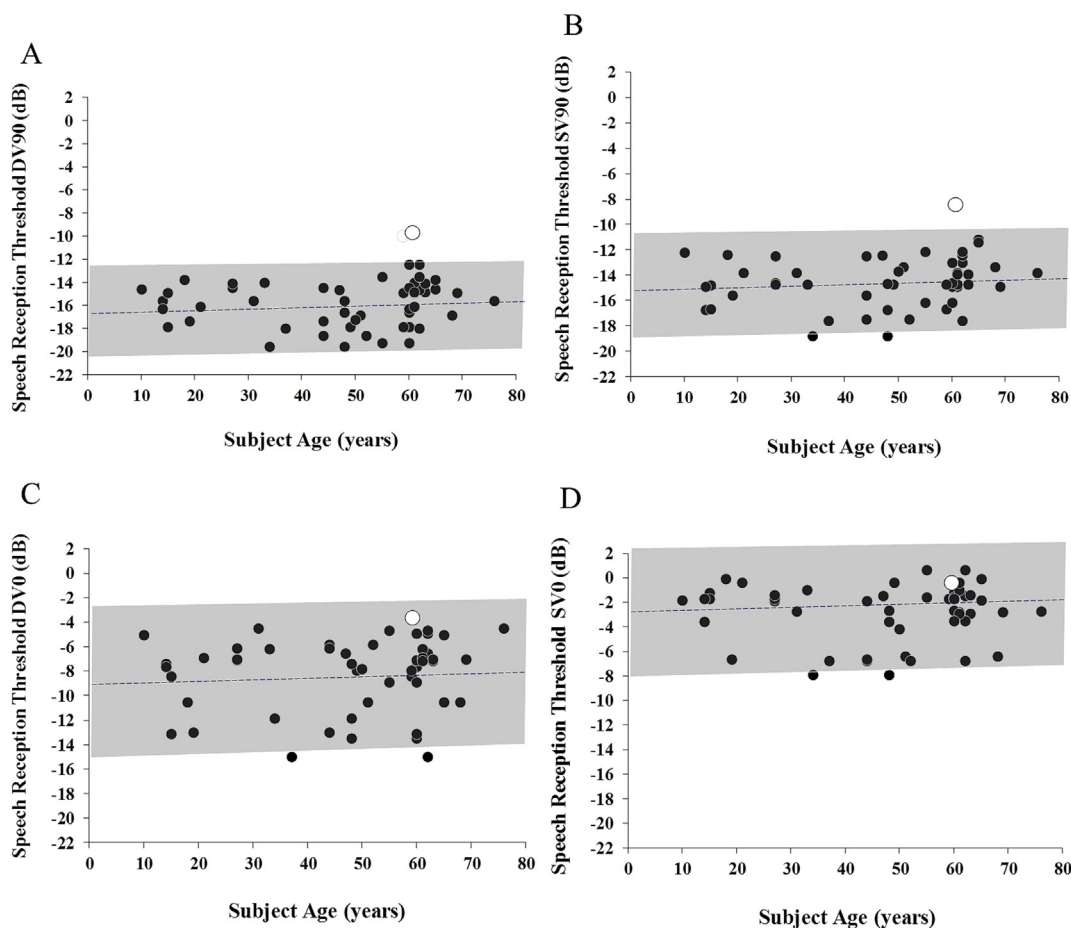
Fig. 4. Binaural speech perception in noise results for Subject DM (unfilled data points) and for a cohort of hearing-level matched controls. Panels A and B show listening conditions in which the target speech and noise are spatially separated (A: different voices with noise and signal separated by 90°; B: same voice with noise and signal separated by 90°). Panels C and D show conditions in which the speech and noise emanate from the same direction (C: different voices with noise and signal separated by 0°; D: same voice with noise and signal separated by 0°). The shaded area in each case represents the mean ± 2 SD range for the control cohort.

1983) and multiple sclerosis (Jacobsen et al., 1987; Pratt et al., 1981; Fowler and Noffsinger, 1983). In the present case, the maximum stimulus rate at which an ABR could be discerned for the left ear was significantly reduced (8 Hz) suggesting that his auditory neural system was more easily stressed beyond its functional capacity than those of the healthy controls. For the right ear, responses could be seen at higher rates (up to 75 Hz), but latency delays were greater than typical, again suggesting the presence of auditory neural dysfunction. The mechanisms underlying this rate vulnerability in our patient are uncertain, but similar patterns have been reported from experimental studies of induced axonal, demyelinating and neuronal synapse disorders (McDonald and Sears, 1970; Saha et al., 1978).

Consistent with this electrophysiologic sensitivity to high rate acoustic signals, Patient DM also showed impaired perception of auditory timing cues. Amplitude modulation detection to high rate stimuli (150 Hz) was poorer than that of healthy controls, indicating an impaired ability to encode signal changes occurring over a brief (6—7 ms) time course. Temporal resolution deficit is common in auditory neuropathy and has been described in patient populations with

demyelinating disease such as Charcot—Marie—Tooth disease (Type 1) (Starr et al., 2003; Rance et al., 2012c) and peripheral nerve axonopathy such as Charcot—Marie—Tooth disease (Type 2) and Friedreich ataxia (Rance et al., 2010, 2012a). In the case of demyelinating neuropathy, the temporal disruption is thought to occur when loss of the neural insulator results in slowed and/or inconsistent conduction of neural signals and a reduced capacity to transmit trains of pulses (Brown and Watson, 2002). Axonopathy may produce temporally inconsistent neural conduction through secondary demyelination and/or conduction block (Brown and Watson, 2002).

The major functional consequence of auditory neuropathy is an impaired ability to hear and understand speech. This deficit occurs primarily because perception of subtle timing differences between phonemes (speech sounds) is crucial to their identification (Rance et al., 2010). As such, the degree of temporal distortion, rather than audibility, is typically the limiting factor in speech understanding (Rance et al., 2004, 2012a, 2012b, 2012c; Zeng et al., 2005). In addition to signal distortion issues, temporal processing deficit also creates particular problems for listening in background noise

(Zeng and Liu, 2006; Rance et al., 2008, 2014). This is thought to occur in part because of a reduced ability to use brief quiet periods in the background noise to access the speech signal (gap listening) (Alcántara et al., 2004) and in part because of an impaired ability to spatially separate sound sources based on interaural timing cues (spatial streaming) (Rance et al., 2012a). The second of these mechanisms was reflected in the findings for Patient DM who showed normal perception when speech and noise were presented from the same direction (i.e. there were no interaural difference cues) but significantly reduced release from masking for conditions in which the signal and noise were emanating from different directions. Where control subjects obtained (on average) a 12 dB improvement in Speech Reception Threshold when speech and noise were separated by 90°, Patient DM was afforded only a 6 dB improvement. This degree of deficit is functionally significant, and in everyday (noisy) listening conditions is likely to impact communication ability, increase stress and impair cognitive function (Hetu et al., 1990).

5. Study limitations

Excessive iron in the auditory system is a plausible aetiology for Patient DMs auditory deficits as pathologic changes to the cochlear nucleus have been demonstrated previously in Hemochromatosis. However, it is possible in this case, that the AN was the result of diabetic peripheral neuropathy. Auditory neuropathy and temporal processing deficit have also been described in patients with Type 1 diabetes (Rance et al., 2014) where the auditory deficit may occur as part of a generalized neuropathic process affecting both the motor and sensory peripheral nervous systems (Callaghan et al., 2012a, 2012b; Rao and Dlouhy, 2012). The exact pathophysiology of peripheral neuropathy in diabetes is yet to be defined, but one or more of polyol accumulation, injury from advanced glycosylated end products (AGEs), and oxidative stress are thought to be involved (Fowler, 2008). As Patient DM had suffered diabetes secondary to the hemochromatosis for 15 years at the time of assessment, and had presented with a neurologic history consistent with Diabetic Peripheral Neuropathy, it is possible that his auditory deficits were, in fact, the result of diabetic sequelae rather than excessive iron deposition. One point of difference between the "typical" diabetic neuropathy pattern and that demonstrated by patient DM is that he only showed ABR changes up to the level of the cochlear nucleus. Diabetic AN usually affects neural conduction in this region and also up to the level of the lateral lemniscus (Parving et al., 1990; Lisowska et al., 2001; Pessin et al., 2008; Rance et al., 2014). This difference may prove to be diagnostically significant, but further data is required.

While the ABR findings for Patient DM indicate abnormality in the VIIIth nerve and brainstem, is it possible that iron-related changes to his brain were not restricted to this region and that his hearing difficulties may (in part) have been caused by lesions at other sites. Hemochromatic changes and concomitant neurological sequelae have, for example, been shown in the central nervous system of affected patients (Lewey and Govons 1942; Neumann, 1948). The degree of CNC involvement in Patient DM was uncertain, but it is well established that other CNS disorders, such as multiple sclerosis can result in auditory (temporal) processing disorder and impaired functional hearing (Furst and Levine, 2015).

6. Summary

Hearing problems have been reported previously in individuals with hemochromatosis, but this study is the first to identify the auditory neuropathy result pattern in an individual with the disorder. The findings of this case study highlight the need for careful audiologic evaluation of patients diagnosed with Hemochromatosis. This is particularly important for individuals (such as Patient DM) who also present with visual deficits as it is well established that combined visual/auditory impairment can have significant cumulative effects on functional status, independence and well-being in patients if unrecognized (Chia et al., 2006).

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