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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.

Keywords: Hemochromatosis; Auditory neuropathy; Temporal processing; Speech perception

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).

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