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Auditory processing deficits in individuals with primary open-angle glaucoma


Abstract
Objective: The high energy demand of the auditory and visual pathways render these sensory systems prone to diseases that impair mitochondrial function. Primary open-angle glaucoma, a neurodegenerative disease of the optic nerve, has recently been associated with a spectrum of mitochondrial abnormalities. This study sought to investigate auditory processing in individuals with open-angle glaucoma. Design/Study sample: Twenty-seven subjects with open-angle glaucoma underwent electrophysiologic (auditory brainstem response), auditory temporal processing (amplitude modulation detection), and speech perception (monosyllabic words in quiet and background noise) assessment in each ear. A cohort of age, gender and hearing level matched control subjects was also tested. Results: While the majority of glaucoma subjects in this study demonstrated normal auditory function, there were a significant number (6/27 subjects, 22%) who showed abnormal auditory brainstem responses and impaired auditory perception in one or both ears. Conclusions: The finding that a significant proportion of subjects with open-angle glaucoma presented with auditory dysfunction provides evidence of systemic neuronal susceptibility. Affected individuals may suffer significant communication difficulties in everyday listening situations.

Key Words: Glaucoma; Auditory neuropathy; Temporal resolution; Auditory processing; Speech perception; Mitochondria

The auditory and optic nerves are involved in several genetic disorders of mitochondrial function including autosomal dominant optic atrophy, Mohn-Tranebjærg syndrome, and Lebers hereditary optic neuropathy (Weiller & Ferbert, 1990; Tranebjærg et al, 1995; Ceranic & Luxon, 2004; Amati-Bonneau et al, 2008; Huang et al, 2009). Glaucoma is a neurodegenerative disease of the optic nerve characterized by the degeneration of retinal ganglion cells and their axons, resulting in permanent vision loss if left untreated. The incidence and prevalence of the disease increases with increasing age and affects up to 10% of individuals over 80 years (Wensor et al, 1998). Primary open-angle glaucoma is the most common form of disease and is diagnosed following clinical evaluation of the anterior segment of the eye with specific confirmation that the angle or area where aqueous fluid drains out from the eye is unobstructed (Weinreb & Khaw, 2004). There is accumulating evidence that primary open-angle glaucoma may result from increased neuronal susceptibility to oxidative stress which may be consequent to mitochondrial dysfunction (Jarrett et al, 2008; Kong et al, 2009). Abu-Amero and colleagues examined the entire mitochondrial coding sequence in a cohort of primary open angle glaucoma patients and reported high levels of mitochondrial DNA changes compared to controls (Abu-Amero et al, 2006). Several studies have investigated the possibility that the neuronal vulnerability observed in the visual systems of glaucoma patients may also manifest in the auditory pathway (Shapiro et al, 1997; Kremmer et al, 2004). However, the focus of these studies has been on the threshold of sound detection which may be normal when percepts dependent on temporal or spectral acoustic cues are disrupted (Starr et al, 1991, 1996). For example, recent work from our laboratory in a cohort of patients with Friedreich ataxia (a mitochondria-based disorder affecting multiple sensory and motor systems) found hearing threshold levels within the normal audiometric range (i.e. sound detection < 20 dB HL) in individuals with severely disordered neural conduction in the central auditory pathways (Rance et al, 2008, 2010a). Electrophysiologic testing in these cases revealed distorted or absent potentials from the cochlear nerve and auditory brainstem consistent with a disruption of the synchrony of neural signals in the auditory pathway. These patients manifested elevated thresholds for detecting rapid changes in auditory signals such as brief gaps in noise and amplitude modulations in continuous sounds. Furthermore, speech understanding, which is dependent on the precise representation of brief timing cues, was severely disrupted such that, in everyday listening conditions (moderate levels of background noise)
many individuals obtained little or no useful auditory information and were forced to rely upon visual cues (lip-reading etc.) to communicate (Rance et al, 2010b). These findings are consistent with the diagnosis of ‘auditory neuropathy’ due to both neural and synaptic disorders of the auditory nerve (Starr et al, 1991; Rance et al, 2004; Zeng et al, 2005).

The possibility of auditory neuropathy and its perceptual consequences has not been specifically examined in subjects with glaucoma. The primary aim of this study, therefore, was to investigate auditory neural function, basic auditory processing, and speech perception ability in a group of subjects with primary open-angle glaucoma. Findings were compared with those obtained from a cohort of age, gender, and hearing level matched individuals in whom the presence of glaucoma had been excluded.

Materials and Methods

Subjects were recruited from the Glaucoma Clinic at the Royal Victorian Eye and Ear Hospital. We included only patients with no self reported history of ear or vestibular disease. Preliminary audiometric screening was also undertaken and only those individuals with sound detection at levels < 40 dB HL at each audiometric frequency participated. Candidates with sound detection beyond this limit were excluded as reduced access to the audiometric frequency participated. Candidates with sound detection at levels beyond this limit were excluded as reduced access to the auditory test stimuli may have confounded the experimental findings (Yellin et al, 1989).

Twenty-seven individuals (16 female) with open-angle glaucoma took part in the study. Mean age for this group was 57.1 ± 9.8 years at assessment. Presence of glaucoma was defined by characteristic optic-nerve head morphology (rim loss and corresponding retinal nerve fibre layer and visual field loss) in the presence of open iridocorneal drainage angles. Tonometry revealed elevated intraocular pressure (> 21 mmHg) in 17 of the subjects. The remaining 10 participants had normal tension glaucoma.

A cohort of control participants matched for age, gender, and hearing level were also recruited for the study. In each case, the age match was within 12 months of a glaucoma counterpart and hearing levels were also recruited for the study. In each case, the pressure (docorneal drainage angles. Tonometry revealed elevated intraocular optic-nerve head morphology (rim loss and corresponding retinal at assessment. Presence of glaucoma was defined by characteristic testor stimuli may have confounded the experimental findings (Yellin et al, 1989).

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A cohort of control participants matched for age, gender, and hearing level were also recruited for the study. In each case, the age match was within 12 months of a glaucoma counterpart and 4-frequency average hearing level was within 5 dB. Mean age for the control group was 58.8 ± 8.8 years. These participants were typically recruited from general ophthalmic clinics at the Royal Victorian Eye and Ear Hospital where each underwent a full eye exam including dilated fundoscopy, visual field analysis, and digital imaging of the optic nerve to exclude glaucoma. Optic nerve assessment included evaluation of optic disc size, neuroretinal rim shape, retinal nerve fibre layer, presence of peripapillary atrophy, and the presence of optic disc haemorrhages. Table 1 shows key differences between subject groups on measures of visual function.

Monaural auditory brainstem response (ABR) testing was undertaken for each subject using an AUDERA evoked potential system. The test stimuli were 100 µs rarefaction polarity, acoustic clicks presented at 90 dBnHL. Stimulus presentation rate was 33.1 Hz. Samples of electroencephalographic (EEG) activity following 2000 stimuli were averaged and at least two separate averages were recorded for each stimulus condition to define response repeatability. Analysis of the averaged activity was completed independently (post-assessment) by two audiologists experienced in ABR waveform interpretation. Measures of absolute and inter-peak latencies for Waves I, III & V were made. The examiners were blinded as to the subject group (glaucoma/control) of each participant.

Auditory temporal resolution was assessed using a task which sought the threshold for detection of sinusoidal amplitude modulation (AM). Each subject was presented with strings of 500-ms duration background signals and trained to respond when (s) he perceived a group of three target stimuli randomly inserted into the sequence (see Rance et al 2010a, for details). The background signals were broadband noise bursts. The modulated (target) stimuli were generated by multiplying the noise burst with a DC-shifted sine wave. Depth of modulation (20 logm) varied from 0 to −30 dB (in −3 dB increments). The rate of modulation was fixed at 150 Hz and the presentation level for all of the stimuli (background and targets) was randomly varied between 82 dB SPL and 88 dB SPL to minimize the possibility that targets could be identified via loudness differences. This presentation range allowed a sensation level of at least 35 dB (re: 4-frequency average hearing level) in each of the test ears. Discrimination threshold was the minimum modulation depth at which the subject could detect the AM on 70% of occasions.

Open-set speech perception ability was assessed using recorded monosyllabic consonant-nucleus-consonant (CNC) words presented to the test ear at 85 dB SPL (rms). The stimuli were presented in two conditions: with the speech stimuli were presented alone; with a competing noise (four-talker babble) presented at the same level as the speech (i.e. 0 dB signal-to-noise ratio) to replicate challenging everyday-listening conditions. The subject’s response to each word was phonetically transcribed and the percentage of phonemes (speech sounds) correctly imitated was calculated.

Results

Preliminary analyses comparing the findings for high tension (N = 17) and normal tension (N = 10) glaucoma subjects revealed no group difference on any of the experimental measures in this study

<table>
<thead>
<tr>
<th>Table 1. Visual characteristics for glaucoma and control subject groups.</th>
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<tbody>
<tr>
<td><strong>Clinical characteristic</strong></td>
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<tr>
<td></td>
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<tr>
<td>Visual acuity (LogMAR)</td>
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<tr>
<td>Visual field mean defect</td>
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<tr>
<td>(decibels)</td>
</tr>
<tr>
<td>Visual field pattern</td>
</tr>
<tr>
<td>sensitivity deviation</td>
</tr>
<tr>
<td>(decibels)</td>
</tr>
<tr>
<td>Average retinal nerve</td>
</tr>
<tr>
<td>fibre layer thickness</td>
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<td>(microns)</td>
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</table>
Auditory brainstem response
Auditory brainstem responses were recordable in each of the individuals who participated in the study. Mean ABR peak latencies for the glaucoma and control groups are shown in Table 2. Paired T-tests showed no difference in wave I and wave III latency between groups (P > 0.05) although there was a trend towards longer wave III latencies in the glaucoma subjects. Mean latency for wave V was significantly longer for the glaucoma cohort (P < 0.005) than matched controls. These differences can be seen in Figure 1 which shows the composite waveforms based upon averaged responses from subjects in the two groups.

ABR interpeak latency (wave I-V) was also prolonged in the glaucoma group (P < 0.01). The distribution of wave I-V interpeak values for each of the glaucoma subjects is shown in Figure 2. These findings suggest that while neural transmission in the auditory nerve and brainstem was relatively normal for most glaucoma cases, 7/54 ears (13%) (six different subjects) did show significantly prolonged latencies. Each of these individuals showed prolonged latencies bilaterally with inter-aural I-V latency differences ≥ 2 msec. Findings for this subgroup with ‘abnormal-ABR’ (represented in Figure 2 by unfilled data points) are considered separately in subsequent analyses.

Amplitude modulation detection
Detection of rapid amplitude changes was significantly poorer for subjects with glaucoma (P < 0.005). Mean AM detection threshold for the glaucoma group was −11.7 ± 2.8 dB (26.1% of the maximum amplitude), and for the matched controls was −14.0 ± 4.0 dB (19.9%). This difference is demonstrated in Figure 3 where detection threshold was beyond the 95% confidence range in 22/54 (41%) of glaucoma cases. Findings for those subjects with ‘abnormal-ABR’ were all below the normal performance limit. Mean threshold for this group (−9.9 ± 2.3 dB) was significantly poorer than for their matched controls (−14.5 ± 4.0 dB) (P < 0.01) and also significantly worse than for the glaucoma subjects with normal ABR (−12.0 ± 2.8) (P < 0.05).

Speech perception
Open-set speech perception ability in quiet was equivalent in the glaucoma and control cohorts, with both groups able to correctly identify and imitate almost all of the target phonemes. Mean CNC-score for the glaucoma group was 94.4 ± 8.1% and for the control group was 94.6 ± 5.5% (P > 0.05). Mean CNC score for subjects in the ‘abnormal-ABR’ group (96.3 ± 92.6%) was equivalent to that of their matched controls (95.3 ± 2.8%) (P > 0.05) and also equivalent to those glaucoma subjects with normal ABR (94.2 ± 8.6%) (P > 0.05).

In contrast, perception of speech signals in the presence of background noise was significantly poorer for the listeners with glaucoma (P < 0.005). Mean CNC phoneme score for the glaucoma group in this condition was 42.1 ± 11.4% and for the matched controls was 47.8 ± 10.9%. Figure 4 shows the distribution of phoneme scores for each of the glaucoma subjects. Subjects with ‘abnormal-ABR’ were typically amongst the poorest performers. Mean phoneme score for this group (32.0 ± 9.0%) was significantly lower than for their matched controls (52.1 ± 10.0%) (P < 0.02), and for those glaucoma subjects with normal ABR (43.3 ± 10.9%) (P < 0.02).

Characterization of the abnormal-ABR group
There were no obvious clinical differences between those glaucoma subjects with abnormal ABR findings and those glaucoma patients with normal brainstem potentials. Group results were equivalent on each of the visual measures (MD/PSD/NFL), indicating a similar degree of optic nerve dysfunction and there were no group differences for age, gender, or average hearing level (P > 0.05).

Discussion
Despite enjoying essentially normal sound detection, a significant proportion of the glaucoma subjects in this study showed abnormal auditory nerve function and auditory processing deficits consistent with impaired representation of timing cues in the central auditory pathways. These data demonstrate that neuronal deficits can exist outside of the visual pathways in primary open angle glaucoma.

Auditory neural function, as reflected by auditory brainstem responses was in fact normal in most glaucoma subjects. Absolute and interpeak latencies in these cases were consistent with those of age, gender, and hearing-level matched controls. Six of the 27 glaucoma participants (22%) did however, show evidence of auditory neuropathy in one or both ears. While the latency of wave I (which reflects the action potential of the auditory nerve) was typically normal in these glaucoma cases, response latencies for subsequent waves (particularly wave V) were significantly increased. This result pattern, which is consistent with a disorder of the axonal component of the auditory nerve, has been reported previously in subjects with mitochondria-related auditory neuropathies (Mondelli et al, 1990; Funalot et al, 1999).

Detection of rapid amplitude modulation was also disrupted in the subjects with glaucoma. In this case a higher proportion of subjects (> 40%) fell outside the 95% performance range, but those individuals with abnormal ABRs tended to show the greatest perceptual deficit. This finding suggests that the central auditory pathways of affected glaucoma listeners have either impaired processing.

<table>
<thead>
<tr>
<th>Subject group</th>
<th>Latency wave I</th>
<th>Latency wave III</th>
<th>Latency wave V</th>
<th>Interpeak Latency (I-V)</th>
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<tbody>
<tr>
<td>Glaucoma (N = 54 ears)</td>
<td>1.48 ± 0.17</td>
<td>3.68 ± 0.14</td>
<td>5.65 ± 0.25</td>
<td>4.17 ± 0.32</td>
</tr>
<tr>
<td>Control (N = 54 ears)</td>
<td>1.47 ± 0.12</td>
<td>3.63 ± 0.19</td>
<td>5.52 ± 0.22</td>
<td>4.04 ± 0.15</td>
</tr>
<tr>
<td>Glaucoma v Control</td>
<td>NS (P &gt; 0.05)</td>
<td>NS (P &gt; 0.05)</td>
<td>P &lt; 0.005</td>
<td>P &lt; 0.01</td>
</tr>
</tbody>
</table>
efficiency (an inability to detect level changes) or a specific deficit in the capacity to encode brief timing cues (Viemeister, 1979). The precise mechanisms underlying this disruption are unknown, but the abnormal electrophysiologic findings point to a disruption in the efficiency of neural firing which could, in turn, have led to a time-smeared representation of the acoustic stimuli (Zeng et al, 2005). We have reported similar deficits in subjects with auditory neuropathies associated with other forms of mitochondrial condition (Starr et al, 1996; Rance et al, 2010a). This is the first report of temporal auditory processing abnormality in glaucoma.

Accurate neural representation of timing cues is crucial for speech perception. In order to understand running speech, or even discriminate sounds within individual words, a listener must perceive the rapid changes that give cues to co-articulation (Rance et al, 2008). For example, perception of acoustic cues lasting only tens of milliseconds (that is, of a similar order to the cues available in the 150-Hz AM detection task) are essential for discrimination of brief consonants. Previous studies involving listeners with severe temporal processing disorders have shown evidence of this level of signal distortion (Rance et al, 2008, 2010a). The finding that speech understanding (in quiet) was normal for the glaucoma subjects in this study (even those with abnormal ABR) indicates a lesser degree of disruption. This is not to suggest however, that they were unimpaired, as speech perception in background noise was significantly depressed in a significant number (approximately 20%) of the glaucoma subjects. Once again those individuals with prolonged neural conduction and abnormal temporal processing were amongst the most affected.

The link between auditory temporal processing deficit and speech-in-noise difficulties is well established (Zeng et al, 2006; Rance et al, 2008) although the mechanisms involved remain unclear. One possibility is that subtle signal distortions, that can be compensated for by linguistic and other redundancies in the speech signal in optimal listening conditions, become more apparent in the presence of background noise. Another is that affected listeners may suffer timing-specific masking effects. Zeng et al (2005) for example, have shown that temporal processing

Figure 2. ABR wave I–V interpeak latencies plotted as a function of age for each of the glaucoma subjects. Each data point shows the result for an individual ear (N = 54). The shaded area represents the 95% confidence range based on findings for the control group. As such, the filled data points represent those glaucoma ears with ‘normal’ I–V interpeak latency (N = 47) and the open points represent those ears with significantly prolonged neural conduction (N = 7).

Figure 3. AM detection threshold plotted as a function of age for each of the glaucoma subjects (N = 54 ears). The shaded area represents the 95% performance range for the control group. The filled data points represent those glaucoma ears with ‘normal’ ABR I–V interpeak latency and the open points represent those ears with significantly prolonged neural conduction.

Figure 4. CNC-phoneme score (0 dB signal-to-noise ratio) plotted as a function of age for each of the glaucoma subjects (N = 54 ears). The shaded area represents the 95% performance range for the control group. The filled data points represent those glaucoma ears with ‘normal’ ABR I–V interpeak latency and the open points represent those ears with significantly prolonged neural conduction.
deficit can affect the ability to separate sounds occurring successively. This could limit a listener’s capacity to use the brief quiet periods in fluctuating background noise to access the speech signal. Whatever the underlying causes, the results of this study indicate that at least some individuals with glaucoma suffer functional hearing difficulties sufficient to impair communication in everyday circumstances (Crandell & Smaldino, 2000).

The pattern of auditory deficits obtained for glaucoma patients in this study resembles that described previously for visual processing in open-angle glaucoma. In both modalities, detection of sensory inputs appears less affected than higher-level processing. In the visual pathway for example, light detection in the peripheral field is reduced later than perception of rapid movement (Tyler, 1981). Similarly, for those subjects in this study with auditory neural disruption, processing of rapidly changing or complex (speech) sounds was impaired despite normal or near-normal sound awareness. Furthermore, consistent with our auditory results, visual psychophysical testing in glaucoma patients has suggested that a loss of temporal resolution may underlie functional deficits (Trick et al, 1995; Shabana et al, 2003).

The presence of auditory processing limitations in some individuals with open-angle glaucoma strongly supports a systemic neuronal susceptibility. The pathophysiology underlying this susceptibility is unclear, but defective mitochondrial function (which can lead to both optic and auditory neuropathies; Abu-Amero et al, 2006; Rance et al, 2008) and which has been implicated in glaucoma (Abu-Amero et al 2006; Jarrett et al, 2008; Kong et al, 2009) is one possibility. Similarity with AN in other established mitochondrial neuropathies further supports the possibility of mitochondrial dysfunction in a subset of optic neuropathies (Cacace & Pinheiro, 2011). Our results suggest that further study of mitochondrial function in glaucoma is warranted.

The clinical implication of these findings is that individuals with one form of known sensory neuropathy may have undetected deficits in other modalities and that these may significantly impair an individual’s ability to communicate. 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), screening tests to detect these deficits should be routinely considered.

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Declaration of interest: The authors declare that they have no competing financial interests or any other form of conflict of interest relating to the study.

References


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MATER DEI HOSPITAL, TAL-QROQQ
Acute General and University Teaching Hospital

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