TITLE PAGE

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Auditory Neuropathy in Individuals with Type 1 Diabetes

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On behalf of all authors, the corresponding author states that there is no conflict of interest.

Auditory Neuropathy in Individuals with Type 1 Diabetes

Structured Abstract

Peripheral neuropathy is a major consequence of diabetes mellitus with up to 50% of patients showing clinically significant neural injury during the disease course. Hearing loss (as defined by impaired sound detection thresholds) is a recognized symptom of DM, but the possibility of auditory neuropathy (AN) has not been explored in this population. This pilot study investigated peripheral auditory function, auditory processing and speech perception in individuals with Type 1 diabetes mellitus (T1DM) and compared the findings with measures of vestibular function, ocular pathology/visual acuity and overall neurologic profile. Ten adults with T1DM and 10 matched controls underwent a battery of tests which included: audiometry, otoacoustic emissions, auditory brainstem responses, temporal processing measures and speech perception. Six of the 10 T1DM participants showed electrophysiologic evidence of AN and impaired functional hearing. Furthermore, auditory capacity was correlated with both visual acuity and degree of somatic peripheral neuropathy.

This pilot investigation revealed functional-hearing deficits severe enough to impact upon everyday communication. Should the findings be confirmed by larger studies, auditory evaluation may form an important part of the management regimen for individuals with T1DM. This may be especially important for those with DM-related eye conditions, as deficits across multiple sensory-modalities can have multiplicative detrimental effects on quality-of-life.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease caused by partial or complete loss of insulin secretion with or without insulin resistance. Type 1 diabetes (T1DM) typically presents in childhood/early adulthood and accounts for 10-15% of all cases.

Peripheral neuropathy is a major consequence of DM with up to 50% of patients showing clinically significant neural injury during the disease course [1]. Typical presentations involve distal symmetric polyneuropathy (DSPN), small-fibre neuropathy and autonomic neuropathy [2]. Somatosensory and visual modalities are commonly affected [2].

Hearing loss (as reflected by abnormal sound detection) is a recognized symptom of DM [3,4]. Proposed cochlear mechanisms include interference of nutrient transportation through thickened capillary walls and flow reductions due to narrowed vessels [5]. Auditory neural changes have also been indicated by electrophysiologic investigations showing delayed brainstem potentials [3] and histologic studies demonstrating VIIIth nerve demyelination and spiral ganglion loss [6,7].

It is well established in other conditions involving the peripheral nerves (Friedreich ataxia, Charcot-Marie-Tooth disease and others) that auditory neuropathy (AN), by affecting the neural representation of complex signals (such as speech), can produce disproportionate perceptual deficits compared with sound detection ability [8-10]. No previous study examining the auditory consequences of T1DM has considered the possible impact of AN on auditory processing and functional hearing.

Our study objectives were to investigate peripheral auditory function, auditory processing and speech perception in individuals with T1DM and to compare these findings with measures of vestibular function, ocular pathology/visual acuity and neurologic profile.

METHODS

This study was approved by the appropriate ethics committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Ten adults with confirmed T1DM participated. All had begun a daily subcutaneous-insulin regimen within two months of diagnosis. Clinical details are shown in Table 1. As each was recruited through a study of diabetes-related eye conditions, most had evidence of ocular abnormality. Diabetic retinopathy, macular oedema and visual acuity levels are shown in Table 1.

Neurological history and physical examination were performed using the Michigan Neuropathy Screening Instrument (MNSI) and Michigan Diabetic Neuropathy Score. Motor and sensory nerve conduction studies were performed in each limb. Neuropathy was defined using clinical and electrodiagnostic results according to minimal-DSPN criteria. Of the 8 patients who underwent full assessment, 6 had symptoms/signs of large-fibre peripheral neuropathy and/or abnormal electrophysiological findings (Table 1). Small-fibre and autonomic neuropathies were investigated using 4-limb cutaneous silent period (CSP) studies, quantitative sudomotor axon-reflex tests (QSART) and cardiovascular Tilt-Table assessment. Seven of 8 participants showed abnormality on one or more of these evaluations (Table 1).

Auditory function was measured bilaterally for each T1DM participant and for 10 healthy, age/gender-matched controls. Sound detection thresholds were established at octave frequencies (250Hz to 8kHz) and a 4-frequency average was calculated for each ear. Distortion-product otoacoustic emissions (DPOAEs) were sought and considered present if response amplitude was ≥6dB for 3 consecutive frequencies.

Auditory brainstem responses (ABRs) were recorded to acoustic-click stimuli presented at 8-, 33-, 57-, 75- and 100Hz. Post-stimulus latency for waves I, III and V and wave V peak-to-peak amplitude were determined.

Temporal resolution was evaluated using an amplitude modulation (AM) detection task [10]. Modulation-depth thresholds were established for AM at 10Hz and 150Hz. Open-set speech perception assessment used CNC-words [9,10]. Stimuli were presented in quiet and speech-in-noise (0dB signal-to-noise ratio [SNR]) conditions.

Horizontal angular vestibulo-ocular (VOR) gain was assessed using the Video Head Impulse Test (vHIT) up to a peak angular velocity of 250°/sec and an angular acceleration of 2000°/sec^2.

RESULTS

Peripheral auditory function was essentially normal in listeners with T1DM. DPOAEs were present in each ear indicating normal cochlear (mechanical) function. Sound detection was mildly elevated

when compared with matched controls (T1DM: 19.2±6.3dBHL; Control: 14.5±6.9dBHL, P=0.003), but average hearing levels were within normal or near-normal ranges in all cases.

Repeatable ABRs were obtained for each T1DM participant to stimuli at the lowest presentation rate (8Hz). Responses were, however, significantly delayed and amplitudes reduced. Absolute peak latencies for wave I were equivalent to controls (T1DM: 1.47±0.11msec; Control: 1.49±0.13msec, P=0.514), but were significantly prolonged for both wave III (T1DM: 3.77±0.31msec; Control: 3.55±0.12msec, P=0.004) and wave V (T1DM: 5.75±0.45msec; Control: 5.31±0.15msec,P<0.001). As a result, neural conduction times (wave I-V inter-peak latencies) were significantly increased (T1DM: 4.28±0.50msec; Control: 3.83±0.15msec, P<0.001). Wave V peak-to-peak amplitude was also attenuated in T1DM participants (T1DM: 0.43±0.17μV; 0.58±0.19μV, P=0.038).

The ABRs of T1DM subjects were more affected by increases in stimulus presentation rate (Figure 1). Mean maximum rate with a recordable ABR for the T1DM group was significantly lower than for the control (T1DM: 74.7±33.0Hz; Control: 97.5±7.7Hz, P=0.009).

Perception of rapid amplitude modulation was impaired. While detection thresholds for low-rate stimuli (10Hz) showed no group difference (T1DM: -19.9±4.3dB; Control: -20.9±3.8dB, P=0.453), high-rate thresholds (150Hz) were significantly higher (worse) in the T1DM group (T1DM: -12.7±7.9dB; Control: -17.0±5.5dB, P=0.025). This pattern is indicative of temporal processing disorder suggesting an impaired capacity to encode brisk signal changes [10,11].

Functional hearing (speech perception) ability was diminished in T1DM-listeners. Significantly lower phoneme discrimination scores were obtained for words in quiet (T1DM: 89.1±9.4%; Control: 94.6±2.6%, P=0.023), and particularly for words in the presence of background noise (T1DM: 38.1±9.8%; Control: 49.2±6.5%, P=0.001). Eight of the 20 T1DM ears showed perceptual ability outside (below) published norms for open-set speech in noise (0dBSNR) [12].

Average bi-directional horizontal VOR gain was within the normal range (>0.68) in all T1DM participants except Case#9, where asymmetric gain indicated unilateral peripheral vestibulopathy (Table 1).

Clinical features, neurologic profile and visual acuity were compared with auditory function for each T1DM participant. There were no correlations between the auditory findings and any of the clinical features (duration of diabetes, age at onset, HbA1c %), clinical neurologic examination (MNSI) or the results of small-fibre and autonomic neuropathy investigation (P>0.05). Both auditory electrophysiologic and perceptual results were, however, correlated with DSPN classification (ABR-rate: r=-0.771, P=0.025; CNC: r=-0.773, P=0.025) and LogMAR score (ABR-rate: r=-0.683, P=0.030; CNC: r=-0.771, P=0.021). That is, those individuals with the most disordered audition were also with the greatest degree of large-fibre peripheral neuropathy and the poorest vision (Table 1).

DISCUSSION

Despite long disease courses (>15 years), neurological history, physical examination and neurophysiological assessment of all participants revealed little or no evidence of peripheral

neuropathy [2]. Notwithstanding this profile, 6/10 T1DM-patients fit the clinical definition for AN showing normal pre-neural responses (DPOAE), absent/abnormal brainstem potentials and impaired functional hearing.

Repeatable ABRs could be obtained (to low-rate stimuli) in all cases, but absolute and inter-peak latencies were increased relative to matched controls. The mechanism(s) are unclear, but reduced conduction efficiency may result from demyelination, which has been reported previously in the auditory nerves of diabetics [6,7]. Response amplitudes were also reduced which may reflect neural dyssynchrony (another possible consequence of demyelination) or axonopathy [8-11].

Abnormal ABRs to high-rate stimuli were observed suggesting that the neural systems of T1DM participants were more easily stressed beyond functional capacity than controls. ABR-rate effects in T1DM-patients have not been described previously, but similar results (ie. loss of the ABR at relatively low presentation frequencies), have been reported for other neuropathologies including mixed-CNS disease and multiple sclerosis [13].

Consistent with this electrophysiologic rate sensitivity, T1DM-listeners also showed impaired perception of timing cues. High-rate AM detection (150Hz) was affected, indicating inefficient coding of signal changes occurring over a brief (6-7msec) time course. Temporal deficit is a cardinal feature of AN and has been described in populations with both demyelinating and axonal neuropathy [8,10,11].

Listeners with T1DM suffered impaired speech perception. As each participant had normal or near-normal sound detection, signal-distortion rather than audibility, was the likely limiting factor. Impaired speech understanding has not previously been reported in T1DM patients, but is common in individuals with AN [8-11]. Perception in background noise was particularly affected. When listening in conditions replicating "everyday" noise-levels, T1DM participants, identified ≈20% fewer speech-sounds than controls. Impaired temporal resolution may explain this result as affected listeners are less able to use brief, relatively quiet periods in a fluctuating environmental-noise to access the speech signal [10,11].

We found no evidence of diabetes-related vestibular dysfunction. The cause of unilateral vestibulopathy in Case#9 is most likely referable to a past history of vestibular neuritis, benign paroxysmal positional vertigo, Meniere's Disease or idiopathic peripheral vestibulopathy. The mismatch between normal vestibular and abnormal auditory findings is unusual, as most conditions resulting in AN tend also to affect the vestibular system [14]. The results suggest that structural differences in the nerves influence their vulnerability in diabetes. While there appears no obvious macroscopic difference in the divisions of the vestibulocochlear nerve, inherent differences in fibre-types may explain the observed functional disparity.

Summary

This study revealed functional-hearing deficits severe enough to impact upon everyday communication. Should the findings be confirmed by larger studies, auditory evaluation may form an important part of the management regimen for individuals with T1DM – even in cases where the overall level of neurologic deficit is relatively mild. While other studies have demonstrated

impaired sound detection, standard audiometry is clearly insufficient as the current results have shown evidence of AN and disordered auditory processing in patients with “normal hearing”. Electrophysiologic evaluation and measures of speech perception are indicated.

Identification of hearing deficit is especially important for individuals with DM-related eye conditions as deficits across multiple sensory-modalities can have multiplicative detrimental effects on independence, social-connectedness and emotional wellbeing if unrecognized [15].

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Table 1. Clinical, neurologic, visual, auditory and vestibular characteristics of participants with T1DM. Visual and auditory results represent the poorer eye and poorer ear.

Case #		1	2	3	4	5	6	7	8	9	10
Features											
Gender		M	M	F	M	F	F	M	F	M	F
Age at disease onset (yrs)		25	13	5	42	24	22	36	25	24	42
Age at assessment (yrs)		41	35	59	57	61	52	58	60	61	60
Disease duration (yrs)		16	22	54	15	37	30	22	35	37	18
HbA1c		8.7	9.4	6.7	8.8	8.2	7.6	8.2	9.2	9.7	7.3
Neurologic											
Clinical Exam	***MNSI***	0	3.5	2	2	0	0	-	0	4	1
Nerve Conduction	***Staged Minimal DPSN***	0 No	1b Confirmed clinical (3)	1b+ Confirmed clinical (3)[@@]	- -	1a Subclinical (4)	1a+ Subclinical (4)[@]	- -	1a Subclinical (4)	1b Confirmed clinical (3)	0 No
CSP		N	A	N	-	N	A	-	A	A	A
Tilt Table		N	A	A	-	A	A	-	N	A	N
QSART		N	N	N	-	N	N	-	N	N	A
Visual											
Diabetic Retinopathy		1	4	3	4	0	0	4	3	4	1
Macular Edema		0	1	2	2	0	0	2	0	2	1
Acuity	***LogMAR***	-0.2	0.2	0.4	0.8	0.1	0.1	0.6	0.0	0.5	0.0
Auditory											
ABR	***I-V Latency***	3.67	3.88	4.46	6.17	4.33	4.04	4.38	3.88	4.48	4.34
	Max Rate	100	100	8	57	100	75	57	100	57	100
Temporal Processing	***AM 10Hz***	-24	-15	-21	-15	-15	-12	-22.4	-16.4	-18	-19.4
	AM 150Hz	-22.4	-19.4	-12.4	-7.4	-13.4	-13.4	-9	-21	-10.4	-21
Speech Perception	***Quiet***	92	97.3	61	84	93.3	90.7	82.7	93.3	91	85.3
	0 dBSNR	47	36	21	18.7	30.7	41.3	37.3	36	34.7	50.7
Vestibular											
VOR gain		1.08	1.01	0.95	0.94	1.04	0.92	*	0.93	0.96	1.03

- HbA1c: glycated haemoglobin (%). Abnormal: >6.5%
- MNSI: Michigan Neuropathy Screening Instrument: number represents score out of a maximum of 8. Abnormal: >0
- Minimal DSPN: Distal symmetric polyneuropathy categorization:
  - [+]1a: Criteria for DSPN met but no signs or symptoms
  - [+]1b: Confirmed clinical Criteria for subclinical neuropathy + neuropathic signs without neuropathic symptoms
  - [@] Subclinical (4): No signs or symptoms of polyneuropathy. Abnormal nerve conduction as per criterion 2 and 3
  - [@@]Confirmed clinical (3): An abnormal nerve conduction study and a symptom or symptoms or a sign or signs of sensorimotor polyneuropathy.
- CSP: Cutaneous silent period classifications. (CSPs depend on Aδ fibres and therefore reflect small fibre function). Abnormal: outside clinic normative values (St. Vincent's Hospital, Melbourne).
- Tilt Table: Cardiovascular autonomic neuropathy rating (blood pressure responses to standing [70^{o} head tilt] recorded via a handgrip dynamometer). Abnormal: outside clinic normative values (St. Vincent's Hospital, Melbourne).

- QSART: Quantitative sudomotor-reflex axon test (acetylcholine iontophoresis with a Q-Sweat machine). Abnormal: outside clinic normative values (St. Vincent's Hospital, Melbourne).
- Diabetic Retinopathy: Scale (0-4) where 0=none and 4= proliferative diabetic retinopathy (modified Airlie House Classification System).
- Macular Oedema: Scale (0-2) where 0=absent and 2=definite (modified Airlie House Classification System)
- LogMAR: Logarithmic minimum angle of resolution. Abnormal: ≥0.3 dB
- ABR: Auditory Brainstem Response
- I-V Latency: conduction time (msec) between wave I and V of the ABR waveform. Abnormal: >4.4 msec
- Max Rate: maximal stimulus presentation rate (Hz) that elicited a discernible ABR waveform. Abnormal: <82.0 Hz.
- Temporal processing: amplitude modulation depth threshold (dB).
  (10 Hz) Abnormal: >-13.3 dB
  (150 Hz) Abnormal: >-6.0 dB
- Speech Perception (Quiet): CNC phoneme score (% correct). Abnormal: <89.5%
- Speech Perception (0dB signal-to-noise ratio [SNR]): CNC phoneme score (% correct) for speech and background presented at the same level. Abnormal: <36.2%
- VOR gain: vestibulo-ocular response. Abnormal: <0.69
- N: normal A: abnormal

Figure 1: Auditory brainstem responses to acoustic click stimuli at presentation rates ranging from 8Hz to 100Hz. Panel A shows tracings for a typical control subject with repeatable waveforms to stimulus rates as high as 75Hz. Panel B shows findings for a T1DM participant (Case#3) where the ABR is only identifiable to clicks at 8Hz. Waves I, III and V are labelled when present.