The role of auditory evoked potentials and otoacoustic emissions in early detection of hearing abnormalities in Behçet's disease patients. A case control study

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ABSTRACT

Objective. *To determine the types and to assess the role of auditory evoked potentials and otoacoustic emissions in early detection of hearing abnormalities in Behçet's disease (BD) patients. Their correlations with disease activity were also considered.*

Methods. *Thirty patients with BD and thirty apparently sex- and age-matched healthy volunteers were included in this study. Auditory evaluation included pure tone audiometry (PTA), otoacoustic emissions (TEOAEs, DPOAE), auditory brainstem response test (ABR) and cortical auditory evoked potentials (tone and speech CAEPs) for all patients and control.*

Results. *The highest abnormality of CAEP latencies elicited by (500Hz and 1000 Hz) as well as speech stimuli (da and ga) among our BD patients was delayed P1 and N1 waves at 80 dB with greater bilateral affection, as well as significant differences between patients and controls. All our BD patients had a smaller amplitude of distortion product OAE (DPOAE) and S/N ratio at 1, 2, 4, 6 kHZ compared with controls and the differences were highly statistically significant (p=0.0001).*

Conclusion. *Being one of the autoimmune inner ear diseases (AIED), BD has a definite hearing impairment, even in the presence of normal hearing sensitivity, as evidenced by PTA. BD patients had a subclinical cochlear pathology which was not affected by disease activity or different organ affection. DPOAE (S/N ratio) proved to be a sensitive test in detecting minimal changes in cochlear pathology and the latencies of CAEPs (tone and speech) measures were considered as sensitive indicators (100%) of early detection of hearing impairment in BD patients.*

Introduction

Behçet's disease (BD) is a systemic inflammatory condition of unknown origin with no definite aetiopathogenetic pathways accepted worldwide (1). As suggested by some authors, BD is considered to be a complex overlapping disorder, sharing both autoimmune and autoinflammatory pathogenetic mechanisms (2). The International Study Group for Behçet's Disease has recommended that recurrent oral ulceration be a prerequisite for a definitive diagnosis, together with two of the following: genital ulcers, skin lesions, eye lesions, and skin hypersensitivity reaction (pathergy test). The presence of other signs, such as arthritis or involvement of the CNS or the gastrointestinal or vascular system, represents minor criteria that may support the diagnosis (3).

Many authors have subsequently reported the involvement of the auditory system and according to several reports, hearing loss in BD occurs between 12% and 80% of cases (4). Many studies encountered a similar autoimmune mediated sensori-neural hearing loss (SNHL) associated with autoimmune diseases such as BD. Researchers reported that cochlear pathology in BD is mainly due to vasculitis of cochlear blood supply (5). Otoacoustic emissions (OAE) are one of many tools that assess cochlear function that was reported to be affected due to vasculitis of the cochlear blood supply in the course of BD (5). Cortical auditory evoked potentials (CAEPs) are used to assess the higher level cognitive processing involved in the discrimination and identification of complex stimuli such as speech sounds and consist of series of long latency auditory evoked

potentials that are composed of positive and negative peaks (P1- N1- P2-N2) occurring between 50 and 300 ms after stimulus onset. Speech evoked P1-N1-P2 (CAEPs) are speech stimuli CV syllable /da/ and /ga/ were also used to study the neural representation of speech-sounds in subjects with impaired speech understanding (6, 7). However, many studies have investigated the auditory involvement in BD but the true data about hearing loss and cognitive function are vague. The aims of this study were to determine the types and degrees of hearing loss and cognitive abnormalities in BD patients and to assess the role of cortical auditory evoked potentials and otoacoustic emissions used in early detection of these abnormalities, as well as its correlation with disease activity.

Subject and methods

Thirty BD patients (23 males and 7 females), satisfying the International Study Group (ISG) criteria (3, 8) and/or the International Criteria for Behçet's Disease (ICBD) (9) were selected from Tanta University Hospital's outpatients clinics, with a mean disease duration of 8.77±6.57 years. Other 30 age- and sex-matched healthy volunteers served as controls. Exclusion criteria were as follows: (i) concomitant otologic diseases leading to sensorineural or conductive hearing loss, such as otorrhea, chronic infective otitis media, congenital hearing loss, congenital anomalies of the head and neck, middle ear effusion; (ii) systemic disorders affecting the ear; as diabetic and hepatitis; (iii) previously administered ototoxic drugs, such as: high dose of salicylate and streptomycin; (iv) history of traumas involving the base of skull; and (v) chronic exposure to acoustic detrimental agents; occupational noise exposure.

Full history taking, clinical examination and relevant investigations were carried out for all patients. Current medications received by the patients were considered and patients receiving corticosteroids were not excluded. Disease activity was assessed according to the method of Aydintug *et al.* (1995) (10). All patients were subjected to full ENT examination and all otoscopic findings were normal, with intact mobile tympanic membranes in both groups.

More specifically, auditory evaluation included pure tone audiometry, otoacoustic emissions and auditory evoked potentials: ILO88 version was performed.

Pure tone audiometry

Pure tone audiometry (PTA) was measured by pure tone audiometer GSI version 61, including air conduction for the frequency range (250-8000Hz) and bone conduction for the frequency range (500–4000 Hz). The threshold was taken as the faintest sound the subject responded to 50% of the time. Hearing thresholds for conventional PTA at any frequency above 25 dB HL was considered as hearing loss (11).

Tympanometry

Tympanometry was conducted and acoustic reflex threshold measurement was elicited contra laterally at frequencies 0.5, 1, 2 and 4 KHz (12).

Otoacoustic emissions

• *Transient evoked otoacoustic emissions (TEOAEs)*

They originate from the outer hair cells of the inner ear. The TEOAEs responses were recorded according to the method of Bray and Kemp (1987), using ILO88 apparatus. (Otodynamics Ltd., Clinical OAE System) cochlear emission analyser. The recordings were assessed with patients motionless with regular spontaneous breathing in a quiet room. Plastic tubing adapters were fitted over the probe housing the sound sources and microphone in order to obtain a good position of the probe in the external auditory canal. On each measurement, 260 stimuli (nonlinear click stimuli) were used. The responses were recorded at 80 dB peak equivalent SPL click stimulus. The frequency spectrum of the TEOAEs responses was in the range of 1000–4000 Hz (13).

• *Distortion product otoacoustic emissions (DPOAEs)*

DPOAEs consist of acoustic emissions in response to two-tonal stimuli. They are the part of the normal process of otoacoustic emission by the cochlea. They does not reflect the stimulus presented to the cochlea totally hence the name Distortion Product. The DPOAE signal extraction method is superior to the TEOAE method above (4000–5000 Hz) and is therefore essential when screening for hearing loss above the speech range. These can have more intensity than the TEOAE click. Therefore, TEOAE should be followed by DPOAEs measurements if the response is deficient (14).

Auditory brainstem response test (ABR)

Four disposable electrodes were fixed according to the Smart EP manual specification as follows: one high frontal Fz (positive electrode), one low frontal Fpz (ground electrode). The last two electrodes were placed on the left and right mastoids (as negative electrode or reference electrode) depending on the recording side. All electrodes were connected to the pre-amplifier of the Smart EP equipment (15).

The stimulus type was click stimuli using analysis epoch (time base or window) that was starting from zero msec before stimulus onset to 12 msec after stimulus presentation, giving a total time window. The number of sweeps in an average is 1024 sweeps, using alternating polarity of stimulus with stimulus intensity that was beginning with 90 dBnHL and descending in 10dB steps until reaching the threshold. The threshold is the lowest signal intensity at which a repeatable response is obtained in 2 out of 3 traces. The filter settings are 150 Hz to 1500 Hz. Stimuli were presented monaurally to both ears via an ER3A insert phone starting with right ear. We comment on three positive waves that are Waves I, III, and V. Their peak latencies are: wave I at 1.6 msec, wave III at 3.6 msec and wave V at 5.6 msec (16, 17).

Cortical auditory evoked response (auditory slow vertex response)

Two types of stimuli were used:

1. *Tone stimuli:* Tones of frequencies 500 and 1000 Hz were used. The rise and fall time of the tone were 10 cycles/sec, and the "plateau" of the tone was

20 ms. The stimulus repetition rate was 0.5 per second (2 stimuli per second) with stimulus intensity that begins with 90 dB nHL and descends in 10dB steps until reaching threshold in each of the previous frequencies. The threshold is the lowest signal intensity at which a repeatable response is obtained in 2 out of 3 traces. The recording window was starting from -50 msec before stimulus onset to 500 msec after stimulus presentation, giving a total time window of about 512 msec. The number of sweeps in an average is 30 sweeps (18).

2. *Speech stimuli:* Speech stimuli CV syllable /da/ and /ga/ were also used. They were pronounced by a native Arabic male speaker. The stimuli were recorded and sent to Intelligent Hearing System Company (IHS) to be digitised and calibrated, with onset frequency of 3900Hz for CV /ga/ and 4200Hz for CV /da/, in which da was a cortical stimulation whereas ga was subcortical stimulation (19). The filter settings were 1 Hz to 30 Hz.pass frequencies higher than 1 Hz. Stimuli were presented monaurally to both ears via an ER3A insert phone starting with right ear (20).

Four disposable electrodes were fixed according to the Smart EP manual specification (15). For each frequency or speech stimuli: the slow cortical response was composed of a positive wave at about 50 ms (P1), a large negative wave at about 80 to 100 ms (N1), and a subsequent positive wave at about 180 to 200 ms (P2). Classically the N2 is a negativity following the P2. Calculation of the latency and amplitude (peak to peak or baseline to peak) of each wave was done as follows: The P1-N1-P2 latency, which was the time from stimulus onset to the first positivity (P1), first negativity (N1), a subsequent positive wave at about 180 to 200 ms (P2), a second negativity (N2). The P1-N1-P2 amplitude, which was typically measured in (uv) from the zero voltage of the trace to the most positive or negative trough in that trace (21).

Statistical analysis

Statistical Package for Social Science (SPSS) programme v. 16 was used for the data analysis. Frequency distribution, tests of significance including chi-squared test, student *t*-test and tests of correlation were used in the analysis. A *p*-value <0.05 was considered significant.

Table I. Demographic data, clinical manifestations and laboratory investigations of BD patients.

Demographic data	Mean±SD	Range
Age (years)	33.47 ± 7.22	23.2-40.5
Disease duration (years)	8.77 ± 6.57	2-15.3
Clinical manifestations	Number=30	Percent %
Recurrent Oral ulcers	30	100
Buccal	30	100
Gingival	13	43.3
Lip	12	40
Tongue	18	60
Genital ulcers (recurrent)	25	83.3
Genital scars	23	76.7
Eye involvement	22	73.3
Anterior uveitis	15	50
Posterior uveitis	10	33.3
Cells in the vitrous fluid	7	23.3
Retinal vasculitis	5	16.7
Conjunctivitis	2	6.7
Optic atrophy	3	10
Skin involvement	15	50
Erythema nodosum	9	30
Pseudofoliculitis	5	16.7
Papulopustular lesions	7	23.3
Acneiform nodules	2	6.7
Pathergy test positivity	8	26.7
Fatigue	20	66.7
Peripheral vascular involvement	16	53.3
Deep venous thrombosis	6	20
Superficial thrombophelebitis	10	33.3
Joint involvement	13	43.3
Arthralgia	13	43.3
Arthritis	5	16.7
Neurological affection	6	20
Headache	5	16.7
Hemiplegia or hemiparesis	4	13.3
Syncopal attacks	2	6.7
Pulmonary embolism	2	6.7
Cardiac involvement (history of infarction)	2	6.7
Laboratoty investigations	Mean ± SD	Range
Hemoglobin (gm/dl)	10.51 ± 1.49	6.3-13.8
Erythrocyte sedimentation rate (1st hour)	68.67 ± 30.78	10-140

Results

Table I shows the demographic, clinical manifestations and laboratory investigations of BD patients. Eleven BD patients (36.7%) had abnormal tympanometric pattern, eight of them (26.6%) had bilateral affection, seven out of eight had type (As) curve and one case (3%) had bilateral type (Ad) curve, while three cases (10%) had unilateral type (As) curve.

Our results found that four patients (13.3%) had abnormal PTA test with unilateral affection more than bilateral affection. All of them had sensorineural hearing loss. With regards to the assessment of cochlear function using OAE in BD patients and healthy controls, all our BD patients had smaller amplitude of distortion product OAE (DPOAE) and S/N ratio at 1,2,4,6 kHZ compared with controls and the differences were statistically highly significant (p=0.0001) (Fig. 1, Table II).

None of our patients had hearing complaint, the percentage of abnormality of CAEP latencies elicited by 500Hz and 1000 Hz in our BD patients varied from 90.0% to 56.7% and from 93.3% to 63.3%, respectively with greater bilateral affection. The highest abnormality was delayed P1 and N1 waves which was (90%) and delayed P1 wave which was (93.3%) at (80 dB) respectively as

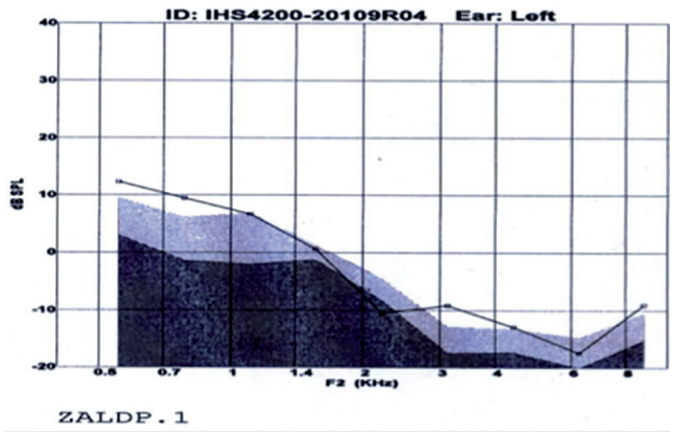

Fig. 1. Absent DPOAEs of left ear of BD patient.

Table II. Comparison between BD patients and control groups as regards OAE (dB SPL) results.

Parameters	BD patients (n=30)	Control (n=30)	*p* value
Transient evoked OAE:			
Response (dB SPL)	4.36 ± 7.04	9.62 ± 4.55	0.005
Reproducibility (%)	30.87 ± 19.54	76.70 ± 13.26	<0.001
Distortion product OAE:			
1 kHz			
Amplitude	8.92 ± 6.31	22.97 ± 5.72	<0.001
S/N ratio	4.36 ± 8.26	19.58 ± 10.70	<0.001
2 kHz			
Amplitude	7.99 ± 6.78	22.07 ± 5.61	<0.001
S/N ratio	11.90 ± 8.73	26.49 ± 6.95	<0.001
4 kHz			
Amplitude	5.59 ± 11.54	24.35 ± 5.25	<0.001
S/N ratio	15.82 ± 10.73	35.59 ± 5.46	<0.001
6 kHz			
Amplitude	4.26 ± 9.07	15.39 ± 10.35	<0.001
S/N ratio	14.65 ± 9.82	25.46 ± 1.81	<0.001

Table III. Comparison between active BD patients and inactive patients as regards OAE (dB SPL) results.

Parameters	Active BD patients (n=17)	Inactive BD patients (n=13)	*p* value
Transient evoked OAE:			
Response (dB SPL)	2.33 ± 0.80	2.61 ± 1.40	0.49
Reproducibility (%)	49.41 ± 6.82	51.21 ± 2.97	0.39
Distortion product OAE:			
1 kHz			
Amplitude	8.68 ± 5.23	9.30 ± 6.67	0.772
S/N ratio	5.16 ± 9.10	5.73 ± 3.92	0.835
2 kHz			
Amplitude	8.50 ± 5.67	9.35 ± 6.60	0.707
S/N ratio	6.50 ± 7.02	10.54 ± 8.66	0.169
4 kHz			
Amplitude	7.27 ± 7.09	7.37 ± 6.14	0.97
S/N ratio	9.55 ± 9.02	13.72 ± 0.63	0.109
6 kHz			
Amplitude	5.75 ± 11.08	5.32 ± 8.36	0.091
S/N ratio	10.64 ± 12.65	15.86 ± 8.77	0.021

well as significant difference between patients and controls (Table IV).

In our study, the percentage of abnormality of CAEP latencies elicited by speech stimulus (da) and (ga) in our BD patients varied from 93.3% to 70% and from 96.7% to 70%, respectively with greater bilateral affection. The highest abnormality was delayed N1 wave at 80 dB which was 93.3% in da stimulus and 96.7% in ga stimulus as well as significant difference between patients and controls (Table III, V).

The highest percentage of absent waves was N2 wave at 80 dB (48.33%). While, the highest percentage of delayed waves was P1 at 80 dB (55%) of unilateral and bilateral ears affection of BD patients as regard CAEPs elicited by 500 Hz. As regard CAEPs elicited by (1000 Hz), the highest percentage of absent waves was P1 wave at (80 dB). While the highest percentage of delayed waves was P1 at 90 dB of unilateral and bilateral ears affection .The highest percentage of absent waves was N2 wave at 80 dB (Fig. 2).

While the highest percentage of delayed waves was N1 at 80 dB of unilateral and bilateral ears affection of BD patients of CAEPs elicited by speech stimulus (da) (Fig. 3). However, the highest percentage of absent waves was N1 wave at 90 dB and N2 wave at 80 dB. While, the highest percentage of delayed waves was N1 at 80 dB of unilateral and bilateral ears affection of CAEPs elicited by speech stimulus (ga) (Table V, Fig. 4).

In this study, seven BD patients (23.3%) had absent tone CAEPs waves, nine BD patients (30%) had absent speech CAEPs and four patients (13.3%) had absent both. The mean duration of BD that had absent CAEPs (tones and speech) in the used frequencies (500 and 1000 Hz) was high (8.77±6.57) but the difference between them and those who had present CAEPs (tones and speech) was statistically insignificant. Comparing the disease parameters in BD patients with and without hearing defect, we found that the patients with hearing impairment had a disease duration of 10.29±5.05 years, which was longer than those with normal hearing (5.30±3.09 years) with a high level of statistical significantce (p=0.003). As regards the effect of age of BD patients on the presence of hearing loss, the patients with normal hearing were younger than those with hearing defects (32.09±7.05 *vs*. 38.00±6.53 years), which was not very statistically significant (p=0.05).

Table IV. Comparison between BD patients and controls as regard CAEPs at stimulus intensity (500& 1000 H z).

		CAEPs (500 Hz)			CAEPs (1000 Hz)		
Intensity(dB)	wave	BD patients mean ± SD	controls mean ± SD	*p* value	BD patients mean ± SD	controls mean ± SD	*p* value
90 dB	P1	59.979 ± 19.402	37.433 ± 4.470	<0.001	54.475 ± 14.329	36.736 ± 4.632	<0.001
	N1	109.745 ± 19.512	82.867 ± 7.72	<0.001	105.000 ± 19.648	81.028 ± 6.986	<0.001
	P2	181.05 ± 20.481	159.433 ± 18.993	<0.001	180.60 ± 26.056	159.692 ± 18.654	<0.001
	N2	253.304 ± 35.513	225.767 ± 37.413	0. 002	247.613 ± 36.725	224.379 ± 24.837	0. 001
80 dB	P1	65.512 ± 21.030	35.484 ± 5.258	<0.001	62.214 ± 14.310	35.958 ± 5.021	<0.001
	N1	120.525 ± 26.458	80.682 ± 7.159	<0.001	112.588 ± 19.819	80.990 ± 7.005	<0.001
	P2	197.462 ± 23.141	158.976 ± 19.012	<0.001	188.758 ± 23.451	158.486 ± 19.257	0.001
	N2	261.097 ± 47.956	249.90 ± 39.529	<0.001	265.154 ± 33.421	254.475 ± 14.329	<0.001

Table V. comparison between BD patients and controls as regard CAEPs elicited by speech stimulus (da & ga).

		CAEPs (da stimulus)			CAEPs (ga stimulus)		
Intensity(dB)	wave	BD patients mean ± SD	controls mean ± SD	*p* value	BD patients mean ± SD	BD patients mean ± SD	*p* value
90 dB	P1	53.967 ± 17.314	38.0 36 ± 3.982	<0.001	53.435 ± 17.924	54.933 ± 16.307	<0.001
	N1	96.267 ± 17.211	81.158 ± 6.921	<0.001	100.964 ± 25.556	102.567 ± 11.422	<0.001
	P2	166.821 ± 31.667	156.200 ± 20.400	<0.001	162.00 ± 22.346	156.633 ± 10.817	<0.001
	N2	225.760 ± 65.941	208.345 ± 12.187	0. 026	222.40 ± 31.854	215.167 ± 9.211	<0.001
80 dB	P1	59.074 ± 26.334	37.574 ± 4.213	<0.001	54.292 ± 12.302	60.379 ± 5.171	0.026
	N1	111.138 ± 27.817	80.784 ± 7.108	<0.001	107.962 ± 14.960	103.200 ± 21.461	<0.001
	P2	177.577 ± 28.347	160.508 ± 18.246	<0.001	181.125 ± 24.662	172.133 ± 32.780	<0.001
	N2	236.708 ± 39.129	210.033 ± 19.132	<0.001	239.952 ± 38.457	228.333 ± 23.473	<0.001

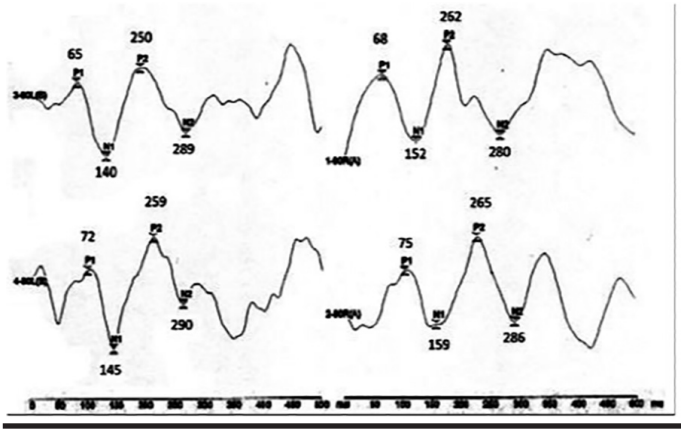

Fig. 2. Bilateral delayed all CAEPs of BD patient elicited by 1000Hz.

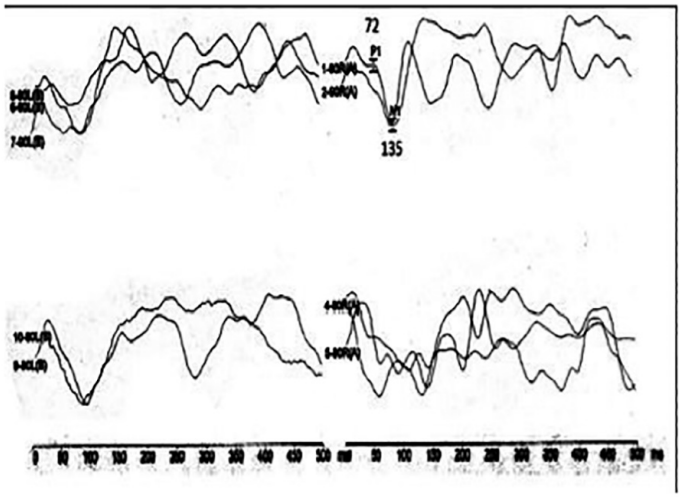

Fig. 3. Rt. Ear: delayed P1&N1 waves and absent P2&N2 waves at (90 dB). Absence of all waves at (80 dB). Lt. Ear: absence of all waves at (90&80 dB) of CAEP elicited by (da) stimulus of B D patient.

Correlation analysis revealed no statistical significance (p>0.05) between the mean age, ESR, and haemoglobin level with either CAEPs or TEOAE. With respect to disease activity, using the Aydintug *et al*. activity score (10), 17 patients were considered to have active disease, while 13 had inactive disease. Comparison of the results of CAEPs between the 2 groups showed that patients with active disease had absent tone and speech CAEPs, but the difference was not statistically significant (p=0.8 and 0.2, respectively). Comparing the results of OAE, patients with active disease had a smaller amplitude and S/N ratio at 1, 2, 4, 6 kHZ, despite not reaching the level of significance (Table III).

Discussion

A number of studies have found that hearing impairment exists in autoimmune diseases, usually at high frequencies (22). The cochlea, saccule, and posterior canal are supplied by the common cochlear artery, while the utricle and anterior and horizontal canals are supplied by the anterior vestibular artery. Outer hair cell function is affected by immunologically mediated

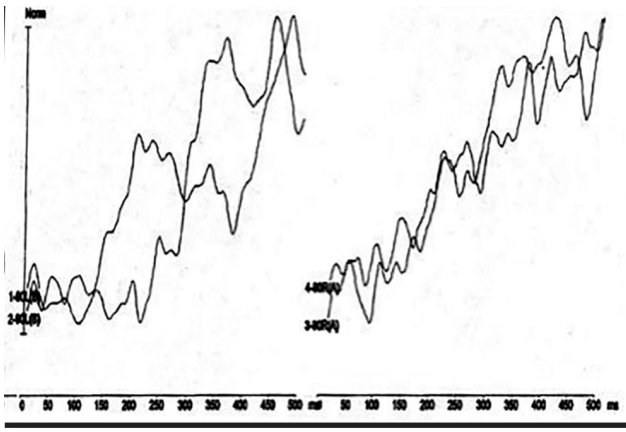

Fig. 4. Absence of all CAEPs elicited by (ga) stimulus.

inflammation of the common cochlear artery (23).

Several studies of autoimmune involvement of the inner ear in BD have been reported that rates of hearing loss among BD patients ranged from 15 to 80% (24). It is interesting that none of the BD patients in our study expressed any complaints about their hearing. This could be explained by having only a mild impairment that had not caused any communication problems in their daily life.

The overall results of many studies which have been conducted in an attempt to determine the precise anatomic location responsible for hearing impairment in BD, have demonstrated cochlear (64% of cases), vestibular (28%), retrocochlear (4%), and external and middle ear (4%) disease involvement (25, 26). In our study, sound-to-noise ratios and reproducibility parameters indicated cochlear disease involvement. None of our patients had retrocochlear involvement, and because we did not perform vestibular testing, we are not able to speculate if any of them had vestibular involvement.

Endolymphatic hydrops (ELH) is an autoimmune inner ear disorder that commonly occurs as a result of imbalance between endolymph production and resorption cycle, which is localised in the stria vascularis and endolymphatic duct and sac respectively. This hydrops might be due to irreversible damage to the sac and duct. However, some studies suggested that immunological mechanisms may be involved in the development of reversible hydrops associated with fluctuating hearing loss in humans (27). According to this concept, the endolymphatic sac is considered to play an essential role as the site of autoimmune response in the inner ear. This response is mostly noticed in the basal turn of the cochlea than the higher turns (28).

OAEs are echo responses derived from presynaptic areas of the auditory system from outer hair cells (OHCs) of the inner ear (29), therefore, were used in our study to detect any minimal lesion in the cochlea that accompanies BD.

In this study, we found that 7 (23.3%) patients had SNHL with mild (16.7%) or moderate (6.7%) degree. Evereklioglu *et al*. reported SNHL in 24% of BD patients and no typical audiogram was observed in 76% of them (30), while in another study, SNHL was reported in 53.8% of 36 BD patients (31).

The TEOAEs results in our research revealed a highly statistically significant difference between BD patients and the control group. This difference may be attributed to immune mediated injury which plays a key role in the development of hydrops with AIED. Willem *et al*. evaluated immune induced AIED in guinea pigs to register low level DPOAE, which has been linked to some active processes responsible for the cochlear sensitivity and frequency selectivity. It is well known that OHCs act as the cochlear amplifier by their unique motor property. The OHCs are also very sensitive to inner ear environment (32). DPOAE both parameters (amplitude and S/N ratio) results revealed a highly significant difference at all frequencies between BD patients and control group in this study.

These findings were supported by previous histopathological studies that reported similar findings by inducing hydrops in the inner ear of guinea pigs to assess its effect on cochlear function using DPOAE. They found a reduction in the DPOAE amplitude (32-34).

The histopathological changes that support cochlear pathology in AIED are signs of a general inflammatory reaction throughout the entire membranous labyrinth, with infiltration of the scala tympani by plasma cells, an extensive membranous labyrinth fibrosis, signs of bleeding in all scalae, a loss of spiral ganglion cells and partial or even complete degeneration of the organ of Corti in all cochlear turns. Remaining intact hair cells were only found in the apex of the cochlea, Reissner's membrane was intact and hydrops did not develop. Deposition of immune complexes and a local cell-mediated immune response are very likely responsible for these extensive inflammatory reactions in the inner ear (35).

Our results were in agreement with Dagli *et al*. who investigated cochlear involvement in 26 BD patients. Their study showed that SNHL was found in 8 patients (30.7%). Although no typical audiometric configuration was found, one patient had a flat type audiogram and the others had a high frequency hearing loss. In our research we found that the DPOAE response of the patients and the controls significantly different in all frequencies, indicating that cochlea is affected by damage of outer hair cells in BD (36). Moreover, results of TEOAE and DPOAE suggest that cochlear pathology in BD patients is centered around the region of 2, 4 and 6kHz (the middle and basal turns of the cochlea) and spares the apical region. These results are in agreement with Bouman *et al*. who reported that electrophysiologic immune-induced changes in the inner ear are mostly noticed in the basal and middle turns of the cochlea than the apical one (28). Moreover, it is in agreement with Sonbay *et al*., who found significant differences in the DPOAE results between the patients and controls at all frequencies ($p<0.05$). These results are a strong indicator of cochlear involvement in patients with BD (24).

In our research we found that there was

a high statistically significant value between BD patients with and without hearing defect and disease duration as the patients with hearing impairment had disease duration longer than those with normal hearing.

As regards the effect of age of BD patients on the presence of hearing loss, the patients with normal hearing were younger than those with hearing defects, which was not statistically significant. This was in agreement with Muluk and Birol, who revealed that as disease duration prolonged, hearing thresholds continue to increase and OAE decrease. Therefore, we believe that disease activity occurring over a long period of duration of disease mediates the occurrence of auditory involvement in BD patients. Contrary to our results, other researches did not find a relationship between disease duration and hearing loss in BD patients (37, 38, 22).

Brama and Fainaru reported that 10 out of 16 BD patients manifesting with hearing loss were older (39). Another study revealed a significant difference between the mean ages of BD patients with and without hearing loss (22). The incidence of orogenital ulcers in our BD patients was high 33.3% and those patients with orogenital ulcers had smaller response and less reproducibility of TEOAE compared to patients without ulcers, but the difference was statistically insignificant. A comparison between the BD patients with normal hearing thresholds and those with hearing defects revealed that patients with hearing defects all had orogenital ulcers 100%, compared to 15 patients 65.2% out of 23 patients with normal hearing thresholds, but the difference was not enough to reach statistical significance. OAE results also revealed that there were no statistically significant differences regarding the presence or absence of different disease manifestations. This was in agreement with other studies that also reported that there was no association between different clinical manifestations and the involvement of the auditory system (30, 37, 38, 40).

This is because BD is a multisystemic disease that affects all organs (including the auditory system) due to its vasculitic aetiology. Although the main underlying pathogenic factor in BD is the autoimmune vasculitis, the mechanisms involved in the pathogenesis of neurological, ocular, cutaneous, vascular and musculoskeletal manifestations may be different. Alternatively, the differential involvement of certain organ system may not reflect the nature of the disease process itself, but rather the manner in which each organ responds to injury (40). This study was also designed to investigate the use of auditory evoked potentials (ABR and CAEPs) in detecting type and site of hearing abnormalities in BD. ABR helps in the diagnosis of the site of lesion and can also help in differentiating cochlear from retrocochlear pathology and to assess the integrity of the auditory periphery and lower brainstem with sensitivity greater than 95%. The ABR is unique among the auditory evoked potentials (AEPs) because of the remarkable reliability of this response (17). In this study, there was delayed latency of wave (V) of ABR in sixteen of BD patients 53.3%. Twelve of them (40%) had bilateral affection while four (13.3%) had unilateral affection. These results agreed with Tugba *et al*. who found delayed latency of wave (V) of ABR in BD patients (41).

ABR is the most commonly applied test of auditory evoked response tests. It has many applications among which the detection of auditory neuropathy and neural conduction disorders because ABR is reflective of auditory nerve and brainstem function. It also provides information regarding auditory function and hearing sensitivity. Prolonged latency of wave (V) as compared with normative data gives rise to the suspicion of retrocochlear pathology (42).

As regards CAEP elicited by (tone and speech) stimuli there were statistically significant differences in CAE latencies in BD patients than in normal individuals in all waves at the used frequencies. None of our BD patients had normal response in CAEPs either in tone or speech in the used frequencies, so the sensitivity of this test is considered to be 100%. Thus, to summarise the previous results, the highest percentage of absent CAEPs of unilateral and bilateral ears affection in BD patients elicited by (500, 1000 Hz) and speech stimulus (da) was N2 wave at 80 dB that varied from 48.33% to 68.33%. While, the highest percentage of delayed latencies of CAEPs of unilateral and bilateral ears affection in BD patients elicited by both speech stimulus (da & ga) was N1 at 80 dB that varied from 27.67% to 43.33%. Auditory evoked potentials can be used to assess the functional consequences of auditory deprivation. By comparing the cortical auditory evoked potentials (CAEPs) of normal-hearing subjects with those of hearing impaired, the functional effects of auditory deprivation on cortical processing can be investigated (43).

RA by way of arteritis or neuropathy could also hypothetically cause sensorineural hearing loss or labyrinthine dysfunction. So, this does not only disrupt the response properties of cortical neurons but may also result in functional reorganisation of cortical activity following permanent sensorineural hearing loss (44).

The duration in BD patients that had absence of CAEPs (tones and speech) in all frequencies was high but the difference between them and those who had CAEPs (tones and speech) was statistically insignificant. In addition, we did not find any statistically significant relationship between disease duration and inner ear involvement, and this is in agreement with Soylu *et al*. (22), Gemignani *et al*. (26) and Brama *et al*. (39), who failed to find any correlation between age, inner ear involvement, and disease duration (40).

In this study, OAE and CAEPs results could not be correlated to disease activity. Few researches were done to study the effect of BD activity on the auditory system. They reported that BD activity was not correlated with audio-vestibular involvement (31, 45).

As with other investigations, our study had certain limitations. First, we did not perform vestibular testing. Second, our sample size was relatively small, and thus we cannot rule out the probability that the incidence of sensorineural hearing loss would have been statistically significant at all frequencies, if we had investigated a larger cohort.

Conclusion

We can conclude from this study that: BD being one of autoimmune inner ear diseases (AIED) has a definite hearing impairment, even in the presence of normal hearing sensitivity, as evidenced by PTA. BD patients had a sub clinical cochlear pathology that was centered around the mid and basal regions of the cochlea as well as retrocochlear pathology and was not affected by disease activity or different organ affection.

DPOAE (S/N ratio) proved to be a sensitive test in detecting minimal changes in cochlear pathology and the latencies of CAEPs (tone and speech) measures were considered as sensitive indicators 100% of early detection of hearing impairment in BD patients.

We would thus recommend the use of OAEs as a regular screening test for cochlear function in BD patients.

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