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RESEARCH ARTICLE

POSSIBLE IMMUNE ALTERATION AFTER COCHLEAR IMPLANTATION

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Abstract

Aims: Cochlear implant (CI) is a widely accepted device to patients with severe to profound sensorineural hearing loss to replace the normal hearing pathway. Since a portion of the device is implanted under the skin, possible immune alteration may occur. Our aim was to assess the production of some selected pro-inflammatory and anti-inflammatory cytokines in patients with cochlear implants and their impact on hearing outcomes.

Material and Methods: Our study was conducted on 25 cochlear implanted patients who were subjected to IL-1β, IL2, IFN-γ and IL6 laboratory assessment preoperatively, postoperatively, 6 months after CI and 2 years after CI. Simultaneously, impedance and neural response telemetry (NRT) were measured and the data were analyzed statistically in relation to the laboratory findings.

Results: No statistically significant difference was found between the levels of cytokines at different times of assessment except a significant increase of IL-1β at first fitting postoperatively in comparison to preoperative sample. Also, no statistically significant difference was found as regards values of impedance and NRT except a significant decrease of postoperative measures of NRT in comparison to intraoperative measures without any malfunction.

Conclusion: There is a minimal immune alteration immediately after CI without any functional affection which may be attributed to the trauma of the implantation surgery rather than foreign body immune response.

Introduction:-

Cochlear implant (CI) is a surgically implanted device to provide a person with moderate to profound sensorineural hearing loss a modified sense of sound. CI bypasses the normal acoustic hearing process to replace it with electric signals which directly stimulate the auditory nerve. A person with a cochlear implant receiving intensive auditorytrainingmaylearntointerpretthosesignalsassound and speech (Clark, 2015).

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Cochlear implants have external (outside) parts and internal (surgically implanted) parts that work together to allow the user to perceive sound. The internal (implanted) parts include a receiver and electrodes. The receiver is just under the skin behind the ear. The receiver takes the coded electrical signals from the transmitter and delivers them to the array of electrodes that have been surgically inserted in the cochlea. The electrodes stimulate the fibers of the auditory nerve, and sound sensations are perceived (Bajaj et al., 2005).

The biologic response to the presence of a biomaterial, whether metal, ceramic or polymeric, is of critical importance to the long-term function of a biomedical implant. It has become clear that although biomaterials may be biocompatible, they are not bio-inert and that a foreign body response is common or universal (Anderson et al., 2008).

Metal-on-metal implants can entail serious complications due to release of wear particles from the implanted material. Metal wear particles presumably activate local host defense mechanisms, which cause a persistent inflammatory response with destruction of bone followed by loosening of the implant (Nadol et al., 2008). The use of cochlear implants involves the following materials coming into contact with the human body: silicone, platinum, titanium and ceramics. Platinum is used as the electrode contact. For the Teflon-coated wires between the receiver/stimulator and the electrode contacts, platinum/iridium 90/10 is used. The wires are embedded in silicone, and thus do not come into contact with human tissue. The electronics within the implant body are housed in a tightly sealed casing which– depending on manufacturer and implant series–is made of either ceramics or titanium (Stöver and Lenarz2009).

Intra-operative monitoring during cochlear implant surgery is a tool to assess integrity of the equipment used and to assess the progress of array introduction and proper placement of the array with subsequent assessment of proper functioning of the device. Furthermore, Intra-operative monitoring is used as a preliminary tool for subsequent CI mapping later on especially for difficult to test patients (Coasetti, 2014).

Two measurements are used: Impedance and Neural response telemetry. Impedance in general refers to the resistance to the flow of energy through any medium. In CI electrode impedance refers to the measure of the opposition to electrical current flow across an electrode and thus, it is influenced by the electrode contact and the electrode lead that is coupled to the contact as well as by the medium surrounding the lead (Wolfe and Schafer 2015).

Impedance measurements are carried out both intraoperative and postoperative during switch-on. These measurements check whether all electrodes function correctly. The analysis of the change in impedance gives an idea about what happens in tissues and liquids of the inner ear around the electrode. In Cochlear implant, the communication between the internal component of implanted electrode and the external speech processor signal is monitored or checked via Custom Sound Software (Wesarg et al., 2014).

Neural Response Telemetry (NRT) gives us clear information about the impedance of the electrode, electrodes position, electrical problems likeshort circuit and open circuit. In addition, failure of electrode during the time of surgery and post- surgery can be monitored (Schulman, 1995). NRT is a method of measuring resistance encountered by electricity passing through wires, electrodes and biological tissue. It is calculated as the ratio of the effective voltage applied to a particular circuit and the actual amount of electrical power intensity (Finley et al., 2008).

Lymphocytes can play a crucial role in the peri-implant "debris-reactivity" environment as well. It is well recognized that T and B lymphocytes are present in peri-implant tissues. The sub types of T cells that dominate implant debris associated responses are T-helper (TH) and not T cytotoxic/suppressor (TC/S). Of the TH cells present, TH1 cells predominate as characterized by production of IFN-γ and IL-2. These TH responses have been characterized as type IV delayed type hypersensitivity (DTH) DTH response to metal implant debris is an adaptive slow cell mediated type of response. Metal-antigen sensitized and activated DTH T-cells release various cytokines which recruit and activate macrophages (Seyyedi and Nadol 2014). Such immune response to implants is commonly reported in many studies.

Objectives: -

The aim of work was to monitor the production of some selected pro- inflammatory and anti-inflammatory cytokines in patients who undergo cochlear implantation and correlate these changes to the hearing outcomes through detection of significant changes in cochlear implant measurements, impedance and neural response telemetry as a result of inner ear pathology after implantation.

Subjects and Methods: -

This study included 25 cochlear implanted patients. Institutional Review Board approval was obtained. Eligibility criteria included the presence of severe to profound sensorineural hearing loss bilaterally and residual hearing thresholds measured by auditory brainstem response or pure-tone audiometry according to patient age in the clinic. Approval for CI by the multidisciplinary team at the Hearing and Speech Institute Imbaba, Giza, Egypt according to established clinical criteria was obtained.

CI devices from two companies (Advanced Bionics and Med-El) approved by the US Food and Drug Administration were eligible to be included in this study.

Impedance measures are done to the array in package aiming at diagnosis of electrode array integrity before being used. Impedances in package are normally high (HI) and abnormality here is: presence of short circuits between any number of electrodes. After electrode insertion, open circuit is usually caused by faulty electrode contacts which will lead to a measurable impedance value at an infinity value indicating that larger amount of current is needed to measure impedances in this specified electrode or may be an indication of broken electrode leads.

Testing impedance multiple times or conditioning (passage of low current through the array) may improve high impedances in Operating room.

Intraoperative impedances were measured on selected electrodes during closure of the incision and before electrically evoked compound action potential measurements. Postoperative impedance was measured during first fitting, on every session of programming and 6 months post operatively.

The ECAP test software from MED-EL was generated as auditory nerve response telemetry (ART) while software from Advanced Bionics was generated as Neural response imaging (NRI).

Neural response Telemetry (NRT) was recorded intra operatively to measure the ECAP thresholds (NRT) on selected electrodes, as a routine part of the cochlear implantation surgery. ECAP measurement took place after implantation of the cochlear implant intraoperatively and 6 months later using Auto-NRT software.

For the assessment of the laboratory parameters, four samples were taken from each patient: first sample was taken one hour pre-operatively. The second sample was taken during the first fitting while the third was 6 months after implantation and the fourth was 2 years postoperatively. Five ml of venous blood were collected from each subject in each session in a plain tube, allowed to clot for 30 minutes and then centrifuged at 3000 round per min (rpm). The serum from each subject was collected individually and stored at -20˚C as a liquots until use. All these samples were subjected to quantitative determination of IL-1β, IL-2, IFN-γ and IL-6 by the use of kits provided by Biosource Diagnostic Europe S.A., Belgium.

The principle of this assay depends on ELISA technique using an immobilization antigen, circulating antibody and enzyme-linked specific antibody (Engall 1980). The absorbance was read spectrophotometry at 450-490 nm with reference filter 630-650 nm. ELISA technique was done using semi-automated ELISA system (TC,96, USA). The concentrations were calculated using computer software capable of generating a four-parameter algorithm.

Ethical consent: informed written consent was taken from the parents.

Statistical Analysis:

Results are expressed as mean ± standard deviation. Comparison between variables measured intraoperatively and after 6 months of operation in the same group was performed using Wilcoxon Signed Ranks test. Comparisons between the lab parameters in the 4 samples with respect to normally distributed numeric variables were done using one-way analysis of variance (ANOVA) followed by Bonferroni posthoc test. Bonferroni correction for p value was used to adjust for multiple testing as appropriate. All p-values are two sided. Statistical Package for Social Sciences (SPSS) computer program (version19 windows) was used for data analysis. P value ≤ 0.05 was considered significant.

Results: -

Comparison between the four tested blood samples as regards the tested immunological parameters (IL1B, IL2, IFN and IL6) revealed that the differences were statistically not significant (Table 1&Fig.1,2,3,4).

Table (1): - Statistical comparison between mean values of the four samples as regards IL-1β, IL-2, IFN-γ and IL-6.

Parameter	1st Sample	2nd Sample	3rd sample	4th sample	ANOVA test	
					F-ratio	p-value
IL1β (pg/ml)	5.15±3.34	7.44 ±4.43	7.09±4.39	5.62±3.15	2.08	0.11
IL2 (pg/ml)	8±4.14	7.67±3.83	7.37±3.7	7.44±3.58	0.14	0.94
IFNγ (pg/ml)	55±23.51	52.7±21.5	55.67±21.86	52.58±22.13	0.13	0.94
IL6 (pg/ml)	30.04±10.65	29.51±9.92	28.9±9.32	27.53±10.78	0.28	0.84

N=25, Data are presented as mean ±SD

P > 0.05 is considered statistically non-significant, P < 0.05 is considered statistically significant.

Figure 1:- Statistical comparison between mean values of the four samples as regards IL-1β.

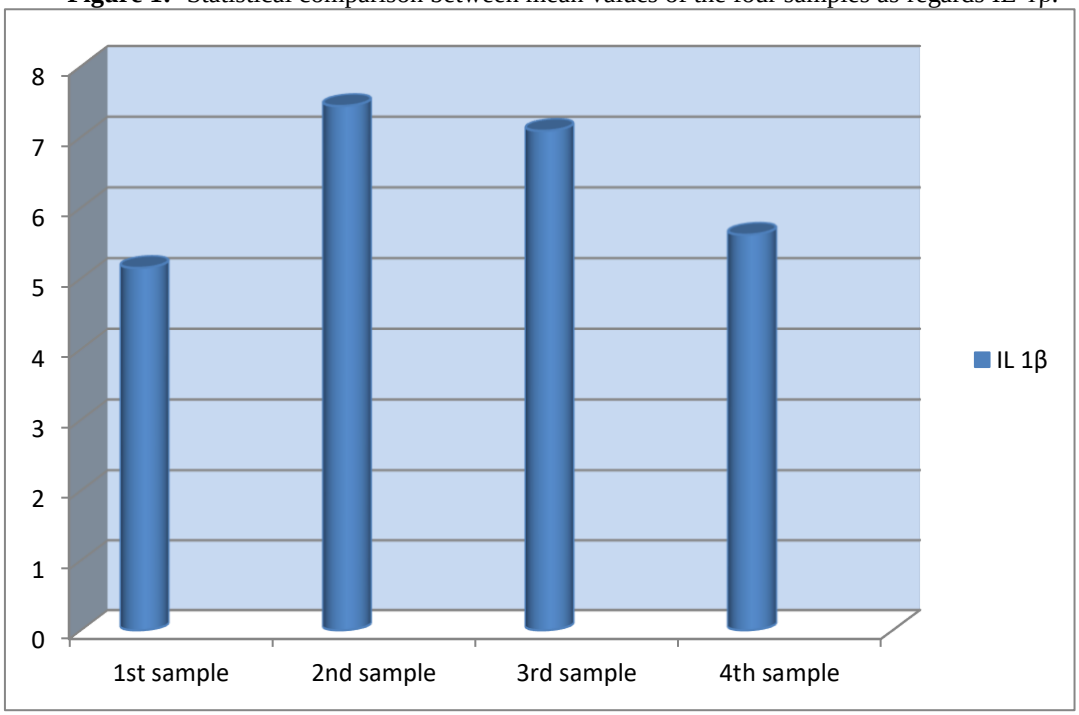

Figure (2):- Statistical comparison betweenmean values ofthe four samples as regards IL-2.

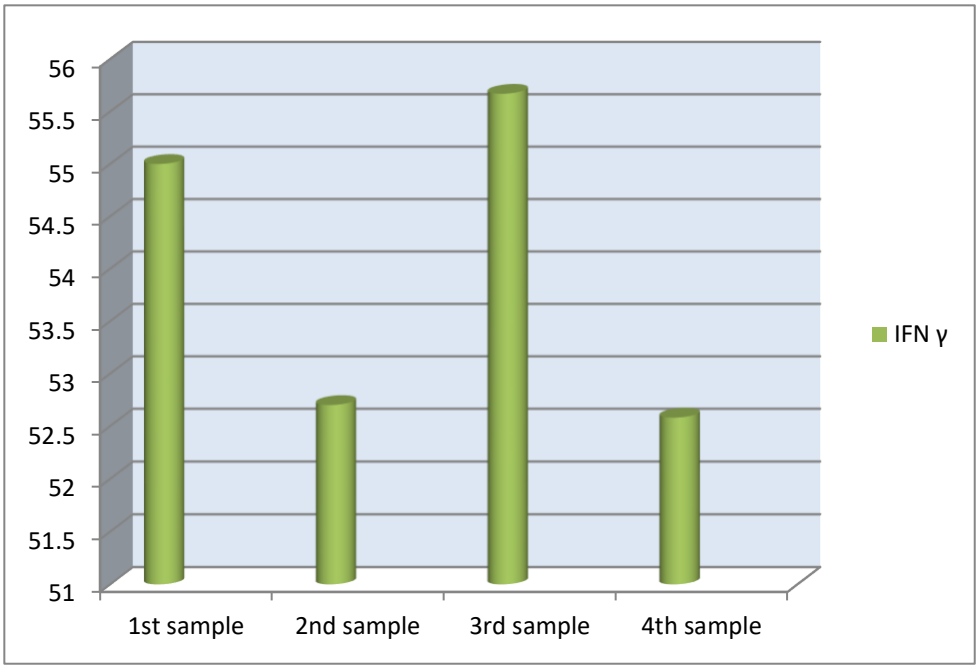

Figure 3:- Statistical comparison between mean values of the four samples as regards IFN-γ.

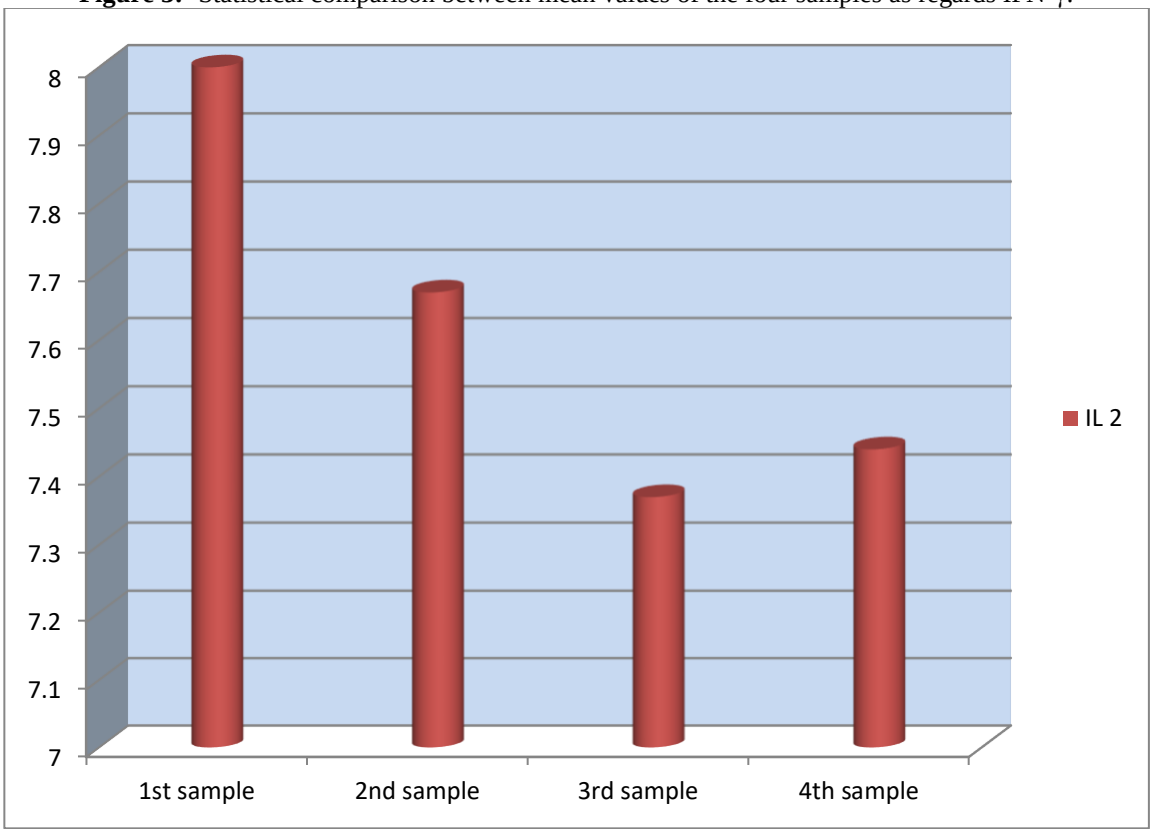

Figure 4:- Statistical comparison between mean values of the four samples as regards IL-6.

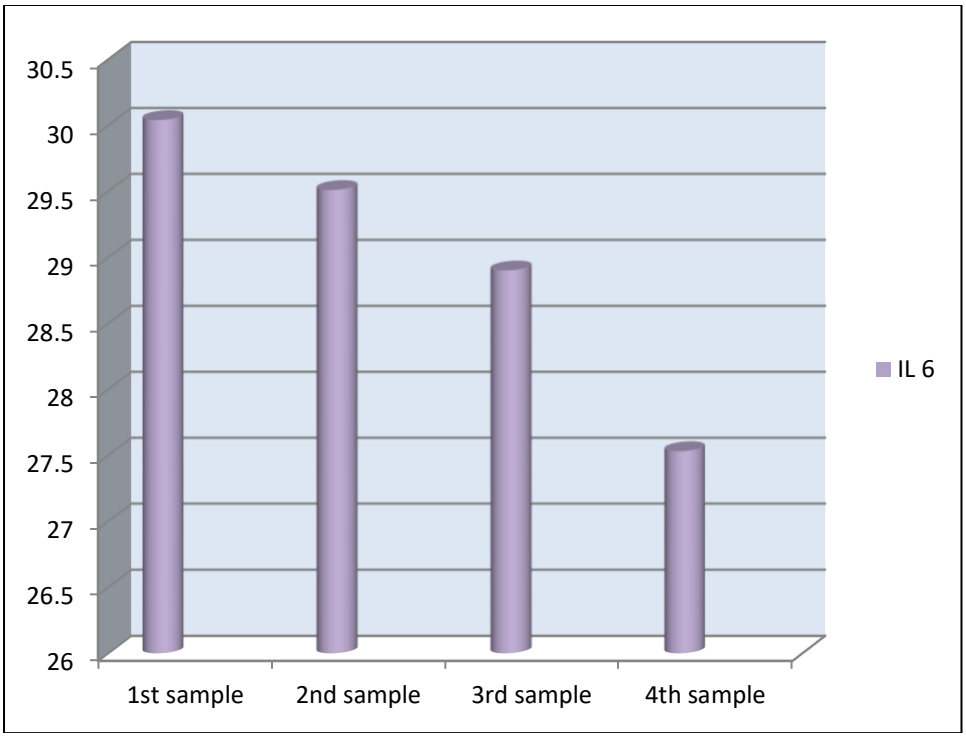

Table 2: - Post hoc test between the 4 samples for each parameter.

	LSD (p-value)					
	1st vs 2nd	1st vs 3rd	1st vs 4th	2nd vs 3rd	2nd vs 4th	3rd vs 4th
IL1β (pg/ml)	0.04*	0.08	0.66	0.75	0.1	0.18
IL2 (pg/ml)	0.76	0.56	0.6	0.78	0.83	0.95
IFNγ (pg/ml)	0.72	0.92	0.7	0.64	0.99	0.63
IL6 (pg/ml)	0.86	0.69	0.39	0.83	0.49	0.64

P > 0.05 is considered statistically non-significant, P < 0.05 is considered statistically significant.

Bonferroni post hoc test was performed to compare the mean value of each 2 samples individually for each parameter. No significant differences were observed except when the1st sample was compared to the 2nd sample for IL-1β ($p < 0.05$). The second sample was significantly higher than the1st one (Table2).

Table 3: - Comparison between values of both impedance and NRT measured intraoperatively and after 6 months in the studied group (number of electrodes=16 advanced Bionics cochlear implant.

	Intra operative (n= 10)	After 6 months(n=10)	Ztest	p value
Impedance	4.61 ± 3.30	5.02 ± 1.16	-0.764	0.445

NRT	186.70±52.80	139.60±53.42	-2.805	0.005*

Data are expressed as mean ± SD, Z= Wilcoxon Signed Ranks test.
P>0.05 is considered statistically non-significant, P<0.05 is considered statistically significant.

Table (4): - Comparison between values of both impedance and ART measured intraoperatively and after 6 months in the studied group (number of electrodes=12 MEDEL cochlear implant).

	Intra operative (n= 15)	After6 months (n=15)	Ztest	p value
Impedance	5.92 ± 0.84	6.20 ± 0.85	-1.580	0.114
ART	17.26 ± 3.18	12.97 ± 2.47	-2.803	0.004*

Data are expressed asmean ± SD, Z= Wilcoxon Signed Ranks test.

P>0.05 is considered statistically non-significant, P<0.05 is considered statistically significant.

No statistically significant difference was found between values of impedance intraoperatively and 6 months post operatively. As regards NRT a significant difference was found between intra and post-operative measures for the two types of cochlear implant devices (Table 3&4).

Discussion: -

Cochlear implants (CI) have been considered well-tolerated and biocompatible auditory prostheses with a low rate of complications that can restore the hearing of the patients with severe to profound hearing impairment (Benattiet al., 2013, Ding et al., 2009, Ray et al., 2004, Venail et al., 2008). Nevertheless, a number of case reports stated that a pronounce inflammatory/allergic reaction to cochlear implants resulted in implant failure, extrusion, explantation or re-implantation (Franz et al., 2011, Kunda et al., 2006, Puri et al., 2005).

Cochlear implantation is always accompanied by surgical injury, which initiates an acute inflammatory response to the electrode. The acute phase of inflammation may be replaced by a chronic phase due to a foreign body reaction induced by components of the electrode array involving macrophages and their derivatives (Anderson et al., 2008, Kunda et al., 2006, Kumar et al., 2010, Rubin et al., 2011).

Inflammatory responses to implant debris overtime have been attributed to macrophage reactivity and have been the primary focus of investigation over the past 40 years. Recent studies demonstrate a predominance of M1 macrophages in response to implant debris challenge (released metal ions and particles), which produce primarily proinflammatory mediators that affect other local cell around implants. It has been shown that macrophages release a host of M1 associated cytokines after contact with wear debris. These include IL-1α, IL-1β and IL-6 (Migirov et al., 2007).

In the current study, our goal was to detect any possible immunological alteration after CI and correlate these changes to the hearing outcomes. We tested the levels of IL1B, IL2, IFN and IL6 (one hour pre-operatively, during the first fitting, 6 months and 2 years after implantation) and correlated these changes to the hearing outcomes through detection of any significant changes in cochlear implant measurements, impedance and neural response telemetry as a result of inner ear pathology after implantation.

No statistically significant difference was found between values of impedance intraoperatively and 6 months postoperatively with no reported cases of short or open circuit during the same duration reflecting absence of Intracochlear lesions.

Although no statistically significant difference was found as regards values of impedance, an increase in values was reported which may be attributed to the physiological changes and fibrosis that occur within the cochlea due to surgical trauma, finding in agreement with Manolacheet al. (2012).

Our results also agreed with Hamada et al. 2016 who referred this increase in level to the absence of electrical stimulation prior to initial activation of the device post operatively and reported general decrease in values over time but not reaching intra operative measurements levels.

Regarding neural response telemetry, the two types of CI devices showed a significant difference between intra and post-operative measures with the fact of absence of any malfunction or cases needing re implantation due to cochlear implant failure. Results revealed that intraoperative recorded thresholds came higher than those recorded 6 months postoperatively. This statistically significant decline in thresholds came in agreement with several other studies (Gordon et al., 2004, Spivak et al., 2011, Telmesani and Said 2016, Youssif, et al. 2018).

The same findings were observed as regards the serum values of the tested immunological parameters. No significant changes were found between their levels before CI and during 2 years of follow up, except for the IL1 B levels during the first fitting when compared to its preoperative levels without any clinical or audiological positive findings.

An Inflammatory response after cochlear implantation is more common at the cochleostomy site than distal to it, suggesting the role of trauma of insertion as a contributing factor (O'Malley et al., 2017).

An acute inflammatory response promotes secretion of pro-inflammatory cytokines from M1 macrophage (IL1β) which in turn may promote sensory cell loss by apoptosis, necrosis, and necrosis-like programmed cell death. T helper2 and M2 macrophage release anti-inflammatory cytokines that help in cell survival and tissue remodeling (Bas et al., 2015).

Our results revealed only a significant elevation of the second sample of IL1β in comparison to the first sample without other significant differences regarding other cytokines. This indicates a soft tissue inflammatory reaction without hypersensitivity response. However, the inflammation may be due to trauma of insertion rather than a foreign body immune reaction.

So, our data suggests that the duration of implantation, the type of electrode do not have any correlation with the severity of cellular reactions. Similarly, Migirov et al. (2007) did not find any association between the duration of implantation and the presence of foreign body reaction. Nadol et al. (2008) did not find correlation between the presence of foreign body reaction and duration of implantation, type of electrode and the tissue used to seal the cochleostomy.

The severity of the cellular immune response has been demonstrated to be negatively correlated with performance (Choiand Oghalai, 2005) and with the preservation of acoustic hearing following implantation (O'Leary et al., 2013). N one of our cases reported severe cellular immune response.

Conclusion:-

There is a minimal immune alteration immediately after CI without any functional affection which may be attributed to the trauma of the implantation surgery rather than foreign body immune response.

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