

Interrelation between INF- γ levels and severity of electrodiagnostic abnormality in acute phase of Bells' palsy

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Abstract

Background: Studies emphasize on the role of herpes simplex virus and herpes zoster in the pathogenesis of Bell's palsy. Regarding increment of Gamma interferon (IFN γ) level in acute viral diseases, we designed this study to assess the IFN γ levels and its relation to the intensity of neurodiagnostic findings in patients with Bell's palsy.

Method and material: 30 patients in acute phase of Bell's palsy were selected and 5 ml blood was obtained in the first 72 hours after diagnosis and right before the beginning of the treatment. Then Gamma interferon was measured and followed by nerve conduction study (NCS) 6 days after Bell's palsy onset.

Findings: There was no significant relationship between gender of subjects and serum level of Gamma interferon with the intensity of entrapment in O. oculi and O. oris muscles. Also, there was no meaningful relationship between age and gender of patients and symptomatic factors with serum level of IFN γ .

Conclusion: It seems there is no significant relationship between immunoserologic changes (serum level of IFN γ) and electrophysiological indices (NCS) in the acute stage of Bell's palsy.

Keywords: IFN γ , nerve conduction study, Bell's palsy

Introduction

Studies emphasize on the theory of viral infection in Bell's palsy. Serological studies indicate that a high percentage of people with Bell's palsy have antibodies for HSV (compared to control group) [1]. Because there is no clear evidence about increasing the amount of specific antibody in Bell's palsy, the disease can be the result of the delayed activity of the virus. This theory is strengthened by increasing serum interferon at the time of Bell's palsy [2, 3].

Measuring performance of facial nerve in Bell's palsy, using electrical tests like Electroneurography (ENoG) will be accompanied by various errors [4]. The difficulty of judgment about two-sided entraplements, difficulty in inducing electrical stimulation at two points because of a high degree of nerve anastomosis in the parotid gland and short time period between excitations, and complexity of the arrangement of facial muscles are some examples. Gamma interferon (IFN γ) is an important cytokine that plays an important role in determining the type of immune response against foreign invaders and intrinsic factors and is secreted by lymphocytes Th1, CD8 + Tc cells and NK cells. Studies revealed that secretion of Gamma interferon increased by activated T cells in different models of the virus [5]. Recently it was shown that T cells secrete more Gamma interferon in HSV1 infection and it deactivates the HSV1 virus in the nerve ganglia [6, 7].

Evaluation of patients with Bell's palsy has shown the increase in serum levels of IL1, IL6 and TNF- α compared to healthy subjects which represent the activities of the cell-mediated immune system's effective factors. Therefore, this theory suggests that the disease has been occurred due to the humoral immune response against a viral infection [8, 9].

Regarding increment of IFN γ level in the acute phase, specific immune response (T helper) and non-specific immune response (NK cell) of viral diseases [9]; we designed this study to assess the IFN γ level and its relation with severity of NCS abnormalities in patients with Bell's palsy.

Methods: This cross-sectional study was implemented on 30 patients with Bell's palsy in acute phase at Vali-e-Asr university Hospital in Zanjan, Iran. General and demographic information was gathered and 5 ml blood was obtained from patients in the first 72 hours after diagnosis and right before treatment. Blood samples were centrifuged and serum was stored at -80 °C for Gamma interferon level measurement.

We carried out nerve conduction study (NCS) 6 days after onset of Bell's palsy in which the ratio of CMAP amplitude of Orbicularis Oris or Orbicularis Oculi muscles in the affected side to unaffected one was measured (under supramaximal stimulation). The scale of the assessment was CMAP amplitude. Less measured amplitude ratio of affected side to healthy was the indicator of less intensity involvement. These NCS results were categorized into 3 groups: poor prognosis (<10%), moderate prognosis (10- 50%) and good prognosis (>50%). We used Boster Immunoleader EK0373 Elisa kit for assessing the Gamma interferon serum level. Normal range according to instruction was 15-6 pg/ml to 1000 pg/ml and accuracy was 2 pg/ml.

Results

Among 30 patients participating in this study 19 were men versus 11 women with mean age of 45 \pm 17 years (the youngest was 20 years old and the oldest one 80). Having the history of atherosclerotic diseases 9 patients (30%) had a positive documented history of these diseases like diabetes mellitus, hypertension, hyperlipidemia, and stroke or ischemic heart diseases. Facial nerve palsy was seen in 13 patients on the right side (43.3%) and in 17 patients on the left side (56.7%).

Table 1. Frequency distribution of accompanying symptoms

Clinical sign	+/_	N(%)
Diarrhea or flu-like syndrome during the last week before disease	-	(3.3)1
	+	(96.7)29
Postauricular pain	+	(60)18
	-	(40)12
Taste disorders	+	(36.7)11
	-	(63.3)19
Hyperacusis	+	(16.7)5
	-	(83.3)25
Hyperlacrimation	+	(60)18
	-	(40)12

The least serum level of Gamma interferon was 6.5 and the highest level was 19.2 with a mean level of Gamma interferon 10.47 \pm 9.43.

Figure 1. Frequency distribution of levels of Gamma interferon within enrolled subjects

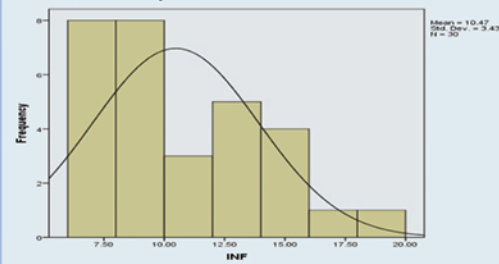
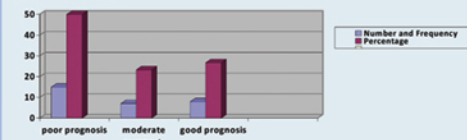


Figure 2. Frequency distribution of patients according to prognosis classification based on the most severity of injury in either the O. oris or O. oculi muscles



Using chi-square test there was no significant relationship between gender and severity of injury in O. oculi muscle ($p=0.325$). We also evaluated this relationship for O. oris muscle and as well as for the highest rate of involvement (based on the NCS) in regards to gender; However, there was not any significant relationship. Studying the relationship between serum levels of IFN γ with age based on the analysis with linear regression test indicated that there was no meaningful relationship between them (P -value=0.426).

Table 2. The relationship between serum level of INF- γ and symptomatic history

Variables	N	Mean of IFN	Standard Deviation	Min	Max	p. value
Familial History	+ 1	-	-	7	7	0.914
	- 29	10.59	3.43	6.50	19.20	
Past Medical History	+ 9	11.13	4.19	7.00	19.02	0.500
	- 21	10.19	3.12	6.50	16.30	
Flue or Diarrhea	+ 1	-	-	-	-	0.948
	- 29	10.46	3.49	6.50	19.20	
Postauricular pain	+ 18	10.45	3.58	6.50	19.20	0.965
	- 12	10.50	3.34	7.00	16.30	
Taste disorders	+ 11	9.11	2.23	7	13.1	0.101
	- 19	11.25	3.80	6.50	19.20	
Hyperacusis	+ 5	9.66	2.86	7	13.10	0.571
	- 25	10.63	3.56	6.50	19.20	
Hyperlacrimation	+ 18	10.88	3.03	7	15.6	0.433
	- 12	9.85	4.02	6.5	19.20	

Key study about the relationship between the serum level of IFN γ and NCS results was done in some domains. First, the relationship between serum levels of Gamma interferon with NCS results in O. oculi and O. oris muscles and the highest number of NCS (in percentage) was evaluated in each patient. Then the relationship between serum level of IFN γ and severity of damage according to the three classes of prognosis in each of the O. oculi and O. oris muscles and maximum final severity were analyzed.

Using linear regression test, there was no relationship between serum levels of IFN γ and NCS results in percentage in O. oculi muscle and in all patients (P -value=0.387). Studying this relationship in O. oris muscle and in all patients based on the coefficient of correlation ($R^2=0.084$) disclosed 8% change of IFN γ is justified with NCS results but there was no relationship via using linear regression test (P -value=0.06).

In linear regression test, the least ratio of CMAP amplitude (highest rate of involvement) in each of the O. oris and O. oculi muscles did not affirm any relationship with serum level of IFN- γ (P -value=0.205). According to the NCS results in O. oculi muscle, mean serum level of IFN γ in poor prognosis group was 9.34 \pm 2.73 with a minimum of 7 and maximum of 14.5. In moderate prognosis group, mean serum levels of Gamma interferon was 12.08 \pm 4.32 with a minimum of 7 and maximum of 19.2. These numbers were 10.1 \pm 3.06, 6.5 and 16.3 in good prognosis group, respectively. Finally, the one-way analysis did not show any meaningful relationship between the intensity of involvement of O. oculi muscle and serum level of IFN γ (P -value=0.218).

Studying the relationship between serum level of IFN γ and maximum severity of damage based on the NCS results in both muscles, mean serum level of Gamma interferon in poor prognosis group was 7.11 \pm 3.58 with a minimum of 7 and maximum of 19.2. In moderate prognosis group, mean serum level of IFN γ was 11.38 \pm 3.23 (minimum= 7; maximum= 15.6) and in the good prognosis group, mean serum level of IFN γ was 9.2 \pm 2.63 (minimum= 5.6; maximum= 13.6). Final analysis via one-way test implied no meaningful relationship between these two variables (P -value=0.459).

Discussion

Jonsson and colleagues in a study in 1989 evaluated serum levels of gamma interferon in patients with Bell's palsy. In the study, levels of IFN γ was evaluated in 91 patients with Bell's palsy. It was shown that level of IFN γ in acute and convalescent phase was significantly increased in patients compared to controls [10]. Their study advantages were larger study size and comparing with the control group, differences in results of two studies are justifiable by these.

In another study by Aviel and colleagues in 1989, they evaluated the serum level of IFN- γ and anti-viral activity in 32 patients with Bell's palsy, after 72 hours from the beginning of the disease. Serum level of Gamma interferon or antiviral activity increased in 23 patients (72%). In this study, normal level of IFN- γ was 16 and the average was 95 which began to decrease 72 hours after onset of disease [8]. Our study has some similar features, such as study size and the time of IFN- γ measurement. But we have not reported our results quantitatively unlike this study.

Our study was consistent with the above study in IFN- γ increment in patients with Bell's palsy. We considered the first 72 hours of an appropriate time interval for evaluating IFN- γ levels. Thus, evaluating the meaningfulness of serum level of IFN- γ increment was not possible because there was no control group in our study.

Ceccanti and colleagues in 2013 studied the predictive role of neurophysiology in Bell's palsy disease. 92 patients were recruited and NCS was carried out for Orbicularis Oris and Orbicularis Oculi muscles. They concluded that amplitude reduction in the affected side compared to the healthy side was related to the outcome of patients with Bell's palsy [11].

In 2014 Takashi and colleagues conducted a study about prognostic factors of Bell's palsy disease in 679 patients. Effects of age, gender, affected side, past medical history, and severity of the disease on the prognosis of patients were assessed. The severity of the disease was relevant to non-healing condition through one week. Age, sex, underlying disease, affected side, and underlying diseases had no relevance with the outcome [12].

In spite of no significant relevance, the noteworthy point was the weak relation between NCS results in O. oris muscle and serum IFN- γ levels. According to P -Value = 0.06 and $R^2=0.084$, 8% changes in gamma interferon level can be described by the NCS results of O. oris muscle. This correlation coefficient shows that these two variables were not associated with the sample size. So it cannot be expected that making the number of samples larger can make significant the relevance. But with the methodological modification, for example by using a control group or follow-up and variables' re-evaluation after 3 weeks, significant results can be expected. Also in this study, most decreased amplitudes were selected among the results of NCS for O. oculi and O. oris muscles and its relevance with serum level of interferon-gamma was evaluated, in which significant relevance was not detected.

In this study, we categorized patients according to NCS results in O. oculi and O. oris muscles and the most decreased amplitude into three prognostic groups: poor, medium, and good; then, relevance with serum level of Gamma interferon was assessed in each group, separately. Based on the current study, there was no significant relationship between variables. Though, regarding high serum level of IFN- γ in patients with Bell's palsy and the relation between involvement severity and NCS results, we expected that there would be an association between these two variables. Considering that serum IFN- γ level is not high in all patients just in few, there is a possibility that low serum level of IFN- γ in some cases is a result of dissociation between these two variables. In other words, it is presumed that if patients with higher than normal serum levels of IFN- γ were enrolled, there would be relations between the serum level of interferon-gamma and involvement severity based on the NCS results.

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