Original Article

The influence of age in peripheral facial palsy on brainstem reflex excitability

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Background: Neuronal plasticity is expected to be different at different ages and adaptive changes developing after peripheral facial palsy (PFP) may provide a clue in this respect. **Aims:** To investigate the difference in the reorganization developing after facial nerve damage between patients who developed PFP at childhood–youth and middle–old age. **Patients and methods:** Twenty-two patients were divided into two groups according to the age-at-onset of PFP; young (PFP 1), and elderly (PFP 2). Two age-matched control groups (C 1 and C 2) comprised of 32 healthy subjects were included in the study. The latency, R_2 area, and recovery of the R_2 area of the blink reflex were investigated. **Statistical analysis**: ANOVA and Bonferroni tests were used. **Results:** The R_2 areas were significantly greater on the intact side of the PFP 1 group as compared to that in the control group (P=0.012). The recovery of R_2 component was significantly enhanced on the symptomatic (P=0.027), and intact (P=0.041) sides in PFP 1 as compared to that in the C 2 group at the stimulus interval of 600 ms. Significant enhanced recovery was noted at 200 ms stimulus interval on the symptomatic side of the two PFP groups (PFP 1, P=0.05 and PFP 2, P=0.025) and on the intact side of the PFP 1 group (P=0.035) as compared to that in the control groups. **Conclusion**: Young age-at-onset of PFP is associated with more prominent excitability changes developing at the neuronal and interneuronal level.

Key words: blink reflex; peripheral facial palsy; recovery of the blink reflex.

Motoneuronal excitability changes on the symptomatic and intact sides have been reported after peripheral facial palsy (PFP) in early and late periods.[1,2] Increased frequency and amplitude of the eye-blink on the intact side or both sides, and later development of blepharospasm in some patients with unilateral PFP may indicate adaptive or maladaptive behavior of the nervous system.[3–6] Elicitation of the contralateral R_1 response following stimulation on the symptomatic side in many cases with unilateral PFP at the regenerative phase was attributed to the synaptic reorganization of the crossing trigemino-facial reflex connections which are functionally suppressed under normal conditions.[7] The changes in the R_2 component of the blink reflex (BR) and its recovery following PFP are considered to provide insight to the functional changes occurring after nerve damage in the motor system.[8] The R_2 response area of the BR, as an indicator of the excitability of the facial motoneurons, is larger on intact side when the stimulus is applied on the symptomatic side in unilateral PFP, contrary to that found in healthy subjects.[1, 9]

PFP can develop at various ages, and one of the factors determining the response of the nervous system to nerve damage is the age-at-onset of the lesion. Therefore, comparing individuals who developed PFP in childhood or youth with those who had developed PFP in middle or old age may provide clues to the influence of age on the reorganization developing after single nerve damage. We studied the area of R_2 component of the BR and its recovery in these two groups of patients with unilateral PFP and evaluated the influence of age on the excitability changes at neuronal and interneuronal levels using BR recovery technique.

Material and Methods

We evaluated retrospectively the EMG recordings of the PFP patients admitted to our EMG laboratory between 2002 and 2004. Patients who have systemic or neurologic diseases, which can affect BR were excluded. The control group consisted of healthy subjects, age-matched with the patient groups. All subjects gave written informed consent to participate in the study after understanding the objectives, and methods of this trial. Local ethical committee was informed of this study and

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ethical clearance was obtained.

Twenty-two subjects with a history of PFP were included in the study. Current ages of the patients at the time of evaluation were between 10 and 69 years, and they developed PFP at the ages between 5 and 66 years. To standardize all parameters except age, only patients with similar PFP durations and clinical presentations were included. All patients had postparalytic overactivity such as synkinesis, and none of them demonstrated persistent complete weakness.

Patients were divided into two groups; 12 patients (56%) (12 women) in the childhood–young age group (PFP 1) and 10 patients (45%) (6 women, 4 men) in the middle–old age group (PFP 2). PFP 1 group developed PFP between 9 and 23 (mean 17.1) years of age (mean evaluation age 18.5). PFP developed between 43 and 66 years (mean 55.6) of age in the PFP 2 group (mean evaluation age 57). Mean PFP duration of both PFP groups were 1.5 years.

Control group 1 (C 1) (50%) (5 men, 11 women) was comprised of subjects between 16 and 29 years of age, and control group 2 (C 2) (50%) (5 men, 11 women) between 45 and 62 years of age.

BR was obtained by electrical stimulation of the supraorbital nerve on both sides with standard methods and it was recorded from both orbicularis oculi muscles, and also from orbicularis oris muscle in order to show synkinetic spread of the reflex response. The cathode was placed over the supraorbital notch. The BR was evoked with a 0.2 ms square-wave pulse at 2.5–3 times the R_2 threshold intensity. Upper and lower frequency bands were chosen as 20 Hz and 1 kHz. Input sensitivity was adjusted as 100–200 μV.[10]

BRs were obtained using paired pulses delivered at 200, 600, and 1000 ms interstimulus intervals. At least 30–35 s was allowed to pass between each stimulus pair to prevent adaptation. The R_2 area was obtained by sweeping the unrectified responses with the area cursor. R_2 area was measured within the window from 32 to 90 ms as explained elsewhere.[11] Latencies were read on the screen with the cursor, and the mean of R_2 areas of five separate responses obtained randomly were evaluated. Recovery of the R_2 area was expressed as a ratio of the mean test R_2 to the mean conditioning R_2 area.

The recordings were performed from symptomatic and intact sides in both PFP patients. Only left sided recordings were obtained in age-matched control patients. The R_1 and R_2 latencies, the R_2 area, and the recovery of the R_2 area values of the BR were accepted as dependent variables.

Statistical analysis

Statistical analysis were performed with the SPSS® 11.5 for Windows™ (SPSS Inc., Chicago, IL). The correlations and comparisons between independent invariables were evaluated by performing two-way ANOVA and Bonferroni tests, as appropriate. Statistically significant P value was accepted as lower than 0.05.

Results

We observed synkinetic movements, and spread of the reflex response to the orbicularis oris muscle in all patients.

BR latencies

The R_1 latencies on the symptomatic sides of both PFP groups were longer than that found in the control groups ($P<0.0001$). The R_2 latencies on the symptomatic sides of PFP 2 group were longer than those in the corresponding control group ($P=0.008$) [Table 1].

R_2 areas

There was statistical significance between the control group and the intact side of the PFP 1 group ($P=0.012$) [Table 1].

BR recovery curve

The R_2 response was suppressed following test stimuli in both PFP and control groups. This suppression was most prominent at 200 ms, and R_2 recovered gradually as the interstimulus interval increase. Suppression was less on both sides in the PFP groups. When PFP 1 group was compared with the C 2 group, there was significant enhancement in recovery at 600 ms on the symptomatic ($P=0.027$) and intact ($P=0.041$) sides. When PFP 1 group was compared with the C 1 group there was significant enhancement in the recovery at 200 ms on the symptomatic ($P=0.05$) and intact ($P=0.035$) sides. When the PFP 2 and C 2 groups were compared, the enhancement in recovery was significant only at 200 ms interstimulus interval on the symptomatic side ($P=0.025$) [Table 1]; [Figures 1 and 2].

Discussion

We investigated whether there is a difference in the reorganization developing after facial nerve damage between patients who developed PFP in childhood or youth and those in middle–old age. The R_1 latencies on the symptomatic sides of both PFP groups were longer than those in their corresponding control groups as expected. We noted a significant increase in the R_2 area, which indicates increased excitability of the facial motoneurons, only on the intact side of the PFP 1 group as compared to that of the control group. Valls-Sole et al. reported increased R_2 area on the intact side when the stimulus is applied on the symptomatic side in unilateral PFP.[1, 9] These findings implicate the development of increased excitability of the facial motoneurons on the intact side after unilateral PFP, and our results showed that this phenomenon is more prominent in younger patients.

Decreased suppression of the R_2 response to the test stimulus using double stimulation paradigm was noted on both sides in the PFP groups. Significant enhanced recovery was reported before on both sides in patients with unilateral PFP.[8] How-

Table 1: The R_1 and R_2 latencies, the R_2 areas and the recovery of the R_2 component at 200, 600, and 1000 ms interstimulus interval of the blink reflex on the symptomatic and intact sides in young and elderly peripheral facial palsy (PFP) patients and on the left side in the corresponding control groups

	Young age groups			Elderly groups			
	Mean±SD	Confidence Interval	d.f.	Mean ± SD	Confidence Interval	d.f.	P
R_1 latency (ms)							
PFP symptomatic side	13.77±2.48	12.1906–15.3428	3	13.44±1.51	12.2843–14.6045	3	
PFP intact side	10.26±1.46	9.4020–11.1130	3	10.19±1.47	9.1384–11.2416	3	
Control group	9.43±0.95	8.9030–9.9610	3	10.28±1.24	9.6208–10.9417	3	
	p<0,001 *, ‡			*p<0,001 ‖, ***			
	p=1,000 †			*p=0,568 ¶*			*P=1,000 ‡‡, ‖*
	p=0,480 §			*p=1,000 ††*			*P=0,866 §§*
R_2 latency (ms)							
PFP symptomatic side	34.74±5.17	31.4595–38.0238	3	36.00±4.69	32.3946–39.6054	3	*p=1.000‡,§§,‖*
PFP intact side	30.67±4.03	28.1124–33.2376	3	32.50±4.06	29.5942–35.4058	3	
Control group	29.83±3.17	28.0710–31.5823	3	31.18±4.31	28.8834–33.4791	3	
	p=0,212 *			*p=0,008 ‖*			
	p=1,000 †,§			*p=0,927 ¶*			
	p=0.030 ‡			*p=0,059 ***			
				p=1,000 ††			*P=1,000 ‡‡, §§,‖*
R_2 area (ms x μ v)							
PFP symptomatic side	4.82±2.94	2.9560–6.6940	3	3.13±2.06	1.5468–4.7198	3	*P=0.309‡‡*
PFP intact side	6.69±3.52	4.4570–8.9263	3	3.84±3.84	1.0906–6.5894	3	*P=1.000§§*
Control group	3.57±1.43	2.8060–4.3315	3	3.62±1.18	2.9938–4.2562	3	*P=0.171‖*
	p=0,309 *			*p=1,000 ‖,¶,**,††*			
	p=0,015 †						*P=0,309‡‡*
	p=0,560 ‡						*P=1,000§§*
	p=0,012 §						*P=0,171‖*
Recovery of the R_2 area							
200 ms (%)							
PFP symptomatic side	34.54±23.71	16.3196–52.7693	3	37.34±20.08	18.7674–55.9164	3	
PFP intact side	32.04±25.48	13.8123–50.2677	3	29.3115.58	14.9061–43.7227	3	
Control group	15.91±7.61	10.4635–21.3565	3	16.34±11.95	8.3182–24.3727	3	
	P=0,050 *,‡			*P=0.025 ‖,***			
	P=0.035 †,§			*P=0.275 ‖*			
				P=0.286 ††			*P=1.000 ‡‡,§§,‡‡,‖*
600 ms (%)							
PFP symptomatic side	69.91±19.20	56.6015–82.0152	3	61.60±34.46	30.2854–92.9146	3	*P=1.000‡‡*
PFP intact side	65.77±23.61	50.7647–80.7686	3	48.1722.97	31.7350–64.6050	3	*P=0.661§§*
Control group	42.46±18.60	32.5461–52.3664	3	56.0622.21	44.2212–67.8913	3	*P=0.180‖*
	P=0.891*			*P=1.000‖,‖,**,††*			
	P=1.000†						
	P=0.027‡						
	P=0.041§						
1000 ms (%)							
PFP symptomatic side	78.46±12.86	69.8234–87.1039	3	53.51±21.39	33.7273–73.3013	3	*P=0.151‡‡*
PFP intact side	65.14±17.46	54.0465–76.2368	3	60.01±23.88	41.6557–78.3666	3	*P=1.000§§,‖*
Control group	59.85±25.39	46.3187–73.3813	3	64.3524.18	51.4630–77.2370	3	
	P=0.676*			*P=1.000‖,**,††*			
	P=1.000†,§						
	P=0.230‡						

*: PFP1 with C1 groups on the symptomatic side, †: PFP1 with C1 groups on the intact side, ‡: PFP1 with C2 groups on the symptomatic side, §: PFP1 with C2 groups on the intact side, Q%: PFP2 with C2 groups on the symptomatic side, ¶: PFP2 with C2 groups on the intact side, **: PFP2 with C1 groups on the symptomatic side, ††: PFP2 with C1 groups on the intact side, ‡‡: PFP1 with PFP2 groups on the symptomatic ide, §§: C1 with C2 groups on the left side

Q%Q%: PFP1 with PFP2 groups on the intact side

ever, the R_2 recovery curves obtained in PFP 1 and PFP 2 groups were different in our study. Increased excitability with interstimulus interval of 200 ms was significant only on the symptomatic side in the PFP 2 group, whereas it was signifi-

cant on both sides in the PFP 1 group. Early recovery of the R_2 response is attributed to the increased excitability or decreased inhibition in interneurons, which participate in the formation of this response. It is known that in conditions in-
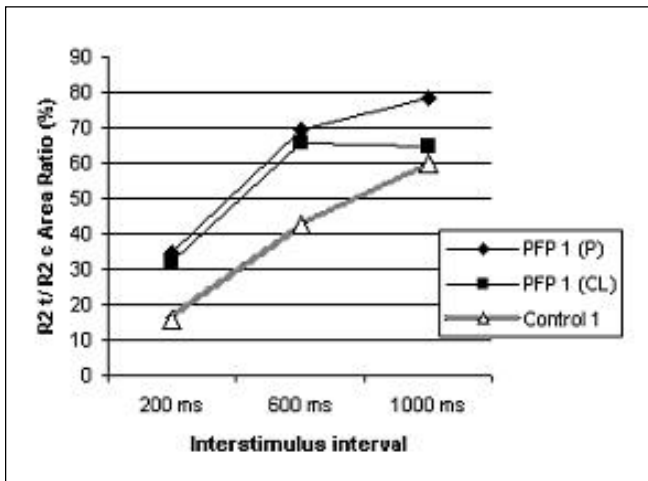
Figure 1: The recovery of the R_2 component of the blink reflex on the symptomatic (P) and intact (CL) sides in young peripheral facial palsy group (PFP 1) and on the left side in the corresponding control (C 1) group. When PFP 1 group was compared with the control group, there was significant enhancement in recovery at 600 ms on the symptomatic side (*P*=0.027), and at 200 (*P*=0.035), and 600 ms (*P*=0.041) on the intact side
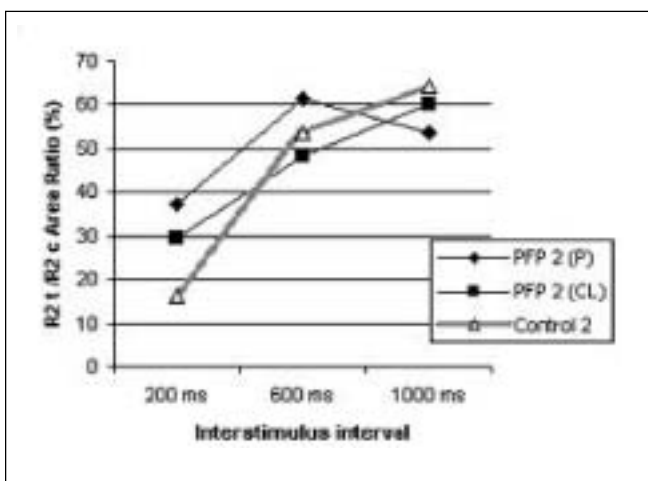
Figure 2: The recovery of the R_2 component of the blink reflex on the symptomatic (P) and intact (CL) sides in elderly peripheral facial palsy group (PFP 2) and on the left side in the corresponding control (C 2) group. When the PFP 2 and C 2 groups were compared, the enhancement in recovery was significant only at 200 ms interstimulus interval on the symptomatic side (*P*=0.025)

volving different levels of the motor system recovery of the R_2 response is more rapid than normal subjects.[12–18]

In essence, we studied the reflex changes occurring after an axonal damage in the facial nerve, and the extent that these changes are influenced by age. Following an axonal lesion, changes such as an increase in the RNA and growth protein synthesis, accelerated metabolism in neurons, and synaptic stripping in the motor neuron membrane are observed.[19, 20] It has been suggested that these changes may cause a decrease in the control exerted by the central-suprasegmental mechanisms on motor neuron firing, and consequently an in-

crease in motor neuron excitability.[21] In addition to the changes in the neurons, microglial activation and vascular changes associated with reactive astrocytosis in the tissue surrounding the neuron also take place.[22–24] Hyper-reactivity of glial cells, and the increase in the pro-inflammatory cytokines following destruction was shown to cause decreased efficiency of repair mechanisms associated with aging of the brain tissue. Increased reactivity of astrocytes has been shown following facial nerve axotomy in aged rats as compared to young rats. In the same study, increased glial fibrillary acidic protein was also shown in the facial nucleus contralateral to the lesion side. The mechanism of this contralateral effect could not be explained.[25]

Sprouting and reinnervation is more extensive and rapid in the developing central nervous system. Aging was shown to be associated with decreased postlesional sprouting capability in animals.[26] Structural and functional changes in the neuronal elements associated with aging, such as the increase in the basal levels of intracellular calcium, is considered as a form of negative plasticity which lead to the decreased efficiency of neuronal networks to accomplish their complex activities.[27]

In conclusion, we have shown that the increased excitability of the BR following PFP follows different patterns in young and elderly subjects. Hyper-reactivity, which may be an adaptive phenomenon, tends to be more intense and bilateral in patients who developed PFP at an earlier age.

References

1. Valls-Sole J, Montero J. Movement disorders in patients with peripheral facial palsy. Mov Disord 2003;18:1424-35.
2. Cossu G, Valls-Sole J, Valldeoriola F, Munoz E, Benitez P, Aguilar F. Reflex excitability of facial motoneurons at onset of muscle reinnervation after facial nerve palsy. Muscle Nerve 1999;22:614-20.
3. Baker RS, Sun WS, Hasan SA, Rouholiman BR, Chuke JC, Cowen DE, et al. Maladaptive neural compensatory mechanisms in Bell's palsy-induced blepharospasm. Neurology 1997;49:223-9.
4. Miwa H, Kondo T, Mizuno Y. Bell's palsy-induced blepharospasm. J Neurol 2002;249:452-4.
5. Chuke JC, Baker RS, Porter JD. Bell's Palsy-associated blepharospasm relieved by aiding eyelid closure. Ann Neurol 1996;39:263-8.
6. Huffman MD, Baker RS, Stava MW, Chuke JC, Rouholiman BR, Porter JD. Kinematic analysis of eyelid movements in patients recovering from unilateral facial nerve palsy. Neurology 1996;46:1079-85.
7. Nacimiento W, Podoll K, Graeber MB, Topper R, Mobius E, Ostermann H, et al. Contralateral early blink reflex in patients with facial nerve palsy: indication for synaptic reorganization in the facial nucleus during regeneration. J Neurol Sci 1992;109:148-55.
8. Syed NA, Delgado A, Sandbrink F, Schulman AE, Hallett M, Floeter MK. Blink reflex recovery in facial weakness: an electrophyisiologic study of adaptive changes. Neurology 1999;52:834-8.
9. Valls-Sole J, Tolosa ES, Pujol M. Myokymic discharges and enhanced facial nerve reflex responses after recovery from idiopathic facial palsy. Muscle Nerve 1992;15:37-42.
10. Kimura J. Electrodiagnosis in disease of nerves and muscles. Principles and practice, 2nd Ed. FA Davis: Philadelphia, 1989.
11. Eekhof JL, Aramideh M, Bour LJ, Hilgevoord AA, Speelman HD, Ongerboer de Visser BW. Blink reflex recovery curves in blepharospasm, torticollis spasmodica, and hemifacial spasm. Muscle Nerve 1996;19:10-5.
12. Ferguson JH. Hemifacial spasm and the facial nucleus. Ann Neurol 1978;4:97-103.

13. Berardelli A, Rothwell JC, Day BL, Marsden CD. Patophysiology of blepharospasm and oromandibular dystonia. Brain 1985;108:593-608.
14. Berardelli A, Rothwell JC, Day BL, Marsden CD. The pathophysiology of cranial dystonia. Adv Neurol 1988;50:525-35.
15. Tolosa E, Montserrat L, Bayes A. Blink reflex studies with focal dystonias. Adv Neurol 1988;50:517-24.
16. Valls-Sole J, Tolosa ES. Blink reflex excitability cycle in hemifacial spasm. Neurology 1989;39:1061-6.
17. Nakashima K, Rothwell JC, Thompson PD, Day BL, Berardelli A, Agostino R, et al. The blink reflex in patients with idiopathic torsion dystonia. Arch Neurol 1990;47:413-6.
18. Evinger C, Bao JB, Powers AS, Kassem IS, Schicatano EJ, Henriquez VM, et al. Dry eye blinking and blepharospasm. Mov Disord 2002;17:S75-8.
19. Griffim JW, Hoffman PN. Degeneration and regeneration in the peripheral nervous system. *In*: Dyck PJ, Thomas PK, Griffin JW, Low PA, Paduslo JF, eds. Peripheral Neuropathy. 3rd Ed. WB Saunders Co: Philadelphia; 1993. p. 361-76.
20. Kreuzberg GW, Raivich G. Neurobiology of regeneration and degeneration. *In*: May M, Schaitkin BM, eds. The facial nerve. Thime: New York; 2000. p. 67-79.
21. Valls-Sole J. Facial palsy, postparalytic facial syndrome, and hemifacial spasm. Mov Disord 2002;17:S49-52.
22. Thomander L. Reorganization of the facial motor nucleus after peripheral nerve regeneration. An HRP study in the rat. Acta Otolaryngol 1984;97:619-26.
23. Nakao Y, Matsumoto K, Kumagami H. Altered distribution of motor neurons in experimental facial nerve paralysis. Acta Otolaryngol 1992;112:998-1003.
24. Baker RS, Stava MW, Nelson KR, May PJ, Huffman MD, Porter JD. Aberrant reinnervation of facial musculature in a subhuman primate: a correlative analysis of eyelid kinematics, muscle synkinesis, and motoneuron localization. Neurology 1994;44:2165-73.
25. Hurley SD, Coleman PD. Facial nerve axotomy in aged and young adult rats: analysis of the glial response. Neurobiol Aging 2003;24:511-8.
26. Nacimiento W, Brook GA, Noth J. Lesion-induced neuronal reorganization in the spinal cord: morphological aspects. Adv Neurol 1997;73:37-59.
27. Kostyuk P. Plasticity in nerve cell function. Aging and neuronal functions. Monographs of the physiological society. Claderon Press: Oxford; 1998. p. 66-82.

Invited Comments

The hyperexcitability after facial palsy in the asymptomatic side is a frequent situation in the early evolution of these patients related with compensatory mechanism.[1,2] The cranial reflexology is a valuable instrument to know it, specially the blink reflex. The hyperexcitability produced in the facial motoneuron pools has been documented in several publication, frequently transitory, and only sometime producing movement disorders.[3,4] The postparalytic blepharospasm is probably the most interesting related situation and several authors have studied them. The increased ipsilateral sensorial inputs provoke a decompensation and subsequently a contralateral trigeminal hyperfunction. These are the more important hypothesis proposed, nevertheless the physiopathology is probably complex and multifactorial (sustantia nigra, cortical influences, peripheral and central synchronization of blink, etc.). The reinnervation after facial axonotmesis and secondarily the central remodelation, are influential factors, undoubtedly more vigorous in youngs because your regeneration mechanisms are more effectives. This condition have a good correlation between the number of blinking motoneurons recruited and the R2 area-amplitude, and this has been confirmed by the paper.[5]

The neurophysiological studies and the animal models are useful instruments to know why the hyperexcitability is produced and how to treat them, but other reflex responses and some electromiographical studies in different situations and lesional periods, are possibilities in the future.

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References

1. Valls-Sole J, Montero J. Movement Disorders in Patients With Peripheral Facial Palsy. Mov Disord 2003;18:1424–35.
2. Valls-Sole J. Facial Palsy, Postparalytic Facial Syndrome, and Hemifacial Spasm. Mov Disord 2002;17:S49–52.
3. Chuke JC, Baker RS, Porter JD. Bell's Palsy-associated blepharospasm relieved by aiding eyelid closure. Ann Neurol 1996;39:263-8.
4. Baker RS, Sun WS, Hasan SA, Rouholiman BR, Chuke JC, Cowen DE, et al. Maladaptive neural compensatory mechanisms in Bell's palsy-induced blepharospasm. Neurology 1997;49:223-9.
5. Kiziltan ME, Uzun N, Kiziltan G, Savrun FK. The influence of age in peripheral facial palsy on brainstem reflex excitability. Neurol India 2005;53:318-22