Ramsay Hunt syndrome: Clinical analysis of 15 cases

George Psillas MD, Jiannis Constantinidis MD, Victor Vital MD, Miltiadis Tsalighopoulos MD

1st Academic ENT Department, Aristotle University of Thessaloniki, AHEPA Hospital

ABSTRACT: *Introduction:* The Ramsay Hunt syndrome (RHS) is characterized by acute facial nerve paresis and/or paralysis accompanied by a herpetic lesion on the external ear.
Material and Methods: Fifteen patients were evaluated and treated for RHS. After a detailed history was obtained, clinical examination was performed, and treatment was initiated based on steroids and acyclovir. The House-Brackmann grading system (HB I-VI) was used to evaluate the facial nerve function; this was further electrophysiologically assessed with the nerve excitability test (NET) and electro-neurography.
Results: In RHS cases, the most common accompanying findings were the cochleovestibular symptoms (73%) and in particular vertigo and balance disorder. The combined treatment of acyclovir with steroids resulted in satisfactory facial nerve function (HB I-II) in 75% of cases. The recovery was satisfactory in all the cases in which the NET was normal or diminished. In 4 cases in which the recovery was non-satisfactory (HB III-V) no response was initially obtained in NET.
Conclusion: In RHS, the possible neuritis and the inflammatory process which occur into the internal auditory canal may result in facial nerve dysfunction and cochleovestibular symptoms. The combined therapy of the antiviral agent acyclovir with the anti-inflammatory effect of steroids is recommended for the treatment of RHS. The NET was proved as the most useful method in the prognostication of RHS.

Key Words: Ramsay-Hunt syndrome, Herpes zoster oticus, Facial paralysis, Acyclovir, Steroids.

INTRODUCTION

In 1907, the Ramsay Hunt syndrome (RHS) was first described by James Ramsay Hunt. It is characterized by acute facial nerve paresis or paralysis accompanied by the presence of herpetic lesions on the external ear (auricle and external auditory canal)[1]. In his original classification, Ramsay Hunt stated that the facial nerve was always the first to be affected in its sensory and/or motor portion; the cochleovestibular symptoms, such as hearing loss, tinnitus or vertigo could also occur. The RHS is caused by reactivation of latent varicella-zoster virus (VZV) in the geniculate ganglion and possibly in the vestibular and spiral ganglia[2].

The VZV is a member of human herpesviruses; it is the etiologic factor for varicella and herpes zoster appearance. Following the primary infection, VZV becomes latent in the cells of the dorsal root ganglia and may be reactivated after a period of several decades; it thus results in the characteristics painful dermatomal rash of herpes zoster. Reactivation is usually associated with depressed cell-mediated immunity, such as in immunosuppressive therapy or HIV infection cases[3]. In herpes zoster, the majority of the morbidity occurs in the elderly and is accompanied by complications such as ophthalmic zoster and post-herpetic neuralgia. The VZV is a ubiquitous infection agent; in a recent publication[4] it was shown that over 50% of young children had antibodies to VZV by their 5th of their age, and over 90% of adolescents were already seropositive for VZV.

VZV has been detected by means of DNA tests in the saliva, tears, cerebrospinal fluid, and peripheral blood mononuclear cells, as well as in vesicles of patients suffering RHS[5]. In RHS, VZV was identified

Corresponding author: Dr George Psillas, 1st Academic ENT Department, Aristotle University of Thessaloniki, AHEPA Hospital, 1, Stilponos Kyriakidi St., GR 540 06 Thessaloniki, Greece, Tel: +30 2310 994762, Fax: +30 2310 994916, email:psillasgeo@the.forthnet.gr

Table 1. The House-Brackmann grading system for the facial paresis or paralysis.

Grade I	Normal facial movement.
Grade II	Slight asymmetry of facial movement.
Grade III	Obvious facial asymmetry; able to close the eye on the affected side.
Grade IV	Obvious facial asymmetry; unable to close the eye on the affected side
Grade V	Only slight movement on the face.
Grade VI	Absence of any movement or tone of the face.

by means of the polymerase chain reaction (PCR) in the geniculate ganglion in the facial nerve sheath[6] on the affected side[7]. Moreover, in RHS patients abnormal enhancement of the facial nerve was identified by magnetic resonance imaging (MRI) scan; this was obvious not only in the facial nerve, but in about 70% of cases in the cochleovestibular nerve and/or the labyrinth as well[8,9]. Compared with the idiopathic facial paralysis of Bell, the severity of the facial paralysis in the RHS cases is worse and its prognosis poorer[10,11]. Among the reported prognostic factors affecting the course of RHS the age[12,13], the initial grading of the facial nerve palsy[12], diabetes mellitus[13], essential hypertension[13] and vertigo[13] are included.

The aim of this study was to present the clinical data of 15 patients suffering from RHS, to evaluate the efficacy of their treatment and to assess the clinical utility of the electrophysiological methods in the prognosis of the disease.

The study was conducted in accordance with the Declaration of Helsinki and the local ethics.

MATERIAL-METHODS

Fifteen RHS cases out of 149 patients suffering of idiopathic unilateral facial paresis or paralysis were retrospectively analyzed. The patients' age ranged from 22 to 80 years. Diagnosis was made on the basis of a) facial paresis or paralysis, b) herpetic lesions in the external ear (auricle and external auditory canal) and c) increase of VZV titers detected by a complement assay during and after the disease.

The treatment was initiated within the first 5 days after the onset of facial paralysis; this consisted of intravenous administration of steroids (prednisolone, 25mgX3/day, and then tapered over 10 days period), and/or oral administration of Acyclovir 800 mg (five times daily for one week). In only one case the antiviral agent Valaciclovir was orally administrated 500 mg two times daily for one week.

The facial nerve function was evaluated on the day of admission, and then 6 months later. The grading of the facial RHS palsy was performed according to the House-Brackmann grading system (I-VI) (Table 1). The recovery of the facial function was characterized as «satisfactory» with HB grade I and II or «non-satisfactory» with HB grade III to VI.

Within the first 10 days after the onset of the disease, the facial nerve function was electrophysiologically assessed with two tests: a) the nerve excitability test (NET) and b) the electroneurography (ENoG). The Myoton 2 Facial Nerve Stimulator was used for the NET examination. The test was initially performed on the healthy side and then on the affected. The current intensity level at which a barely visible muscle twitch was elicited was determined as the NET threshold respectively on both sides. A comparison of the NET threshold between the two sides was made. A difference of 3.5 mA was defined as «normal»; a difference of 3.5 mA or greater between the two sides was defined as «diminished»; whereas no facial reaction was produced the cases were characterized as «no response»[14].

For ENoG, the surface stimulator (Amplaid MK12) was placed over the main trunk of the facial nerve with the anode just outside the stylomastoid foramen and the cathode in front of the ear lobe. The applied current intensity was increased from zero to a maximal level sufficient to evoke the myogenic compound action potential. The percentage of degenerated nerve fibers was calculated by dividing the amplitude of the myogenic compound action potential of the affected side by that of the normal side. The prognosis for recovery to normal facial function was considered poor when the electroneurography showed greater than 90% neural degeneration[15].

Finally, an audiometric assessment was performed in all the patients and a pure tone audiometry was con-

Table 2. Main localizations of the vesicles in RHS.

Localization	Cases
Pinna	8 (53%) (Figure 1)
External auditory canal	2 (13%)
Cervical region	2 (13%) (Figure 1)
Parotid region	2 (13%)
Mastoid area	1 (6%) (Figure 1)
Hard palate	1 (6%)

Table 3. Distribution of accompanying symptoms of RHS among the patient sample (n = 15).

	n	%
Cochleovestibular symptoms	11	73
- Vertigo, instability	9	60
Tear flow	6	40
Taste disorders	6	40
Otalgia	4	26
Headache	4	26
Neck pain	3	20
Numbness in the parotid region	2	13
Vocal cord paresis	1	6

ducted across the frequencies from 250 to 8000 Hz with the GSI-61 audiometer, which was calibrated according to ISO 389 (International Organization for Standardization, 1991).

RESULTS

According to the initial House-Brackmann facial nerve function grading, 9 (60%) patients were characterized as grade V, 1 as grade IV, and 5 as grade III. Four patients exhibited facial paresis (or paralysis) after the appearance of the vesicles, 3 patients developed the vesicles after the onset of facial paresis or paralysis, and in 8 cases the facial paresis (or paralysis) and the vesicles appeared simultaneously. The main localizations of vesicles are shown in Table 2.

The most common accompanying symptoms were cochleovestibular (73%) (Table 3). In particular, vertigo and balance disorder occurred in 9 (60%) patients. Tinnitus was reported in 5 patients. Four patients had sensorineural hearing loss (moderate to severe sensorineural hearing loss in 2 patients, one patient had high-frequency hearing loss; one patient had ipsilateral anacusis).

In 11 (73%) out of the 15 patients, the facial nerve recovered satisfactorily in 6 months after the treatment. However, in 4 patients the recovery was non-satisfactory (Figure 2). Twelve patients were treated with acyclovir in combination with steroids (Table 4); 9 (75%) out of these 12 patients recovered to grade I and II.

In 6 cases, the recovery was complete (grade I); one patient remained to grade V. It was noticed that the recovery was satisfactory in half of the cases in which the initial facial paralysis was complete (grade V). According to the history, the first signs of recovery were observed in the time span of 7 to 30 days after the onset of RHS. In the cases that recovered to grade III a certain form of synkinesis occurred in the long-term (after 6 months).

The recovery was satisfactory in all the cases in which the NET was normal or diminished (Table 5). In 4 cases in which the recovery was non-satisfactory no response was initially obtained in NET. In one case, although the ENoG showed less than 90% of degeneration the outcome was poor (grade III), and in 4

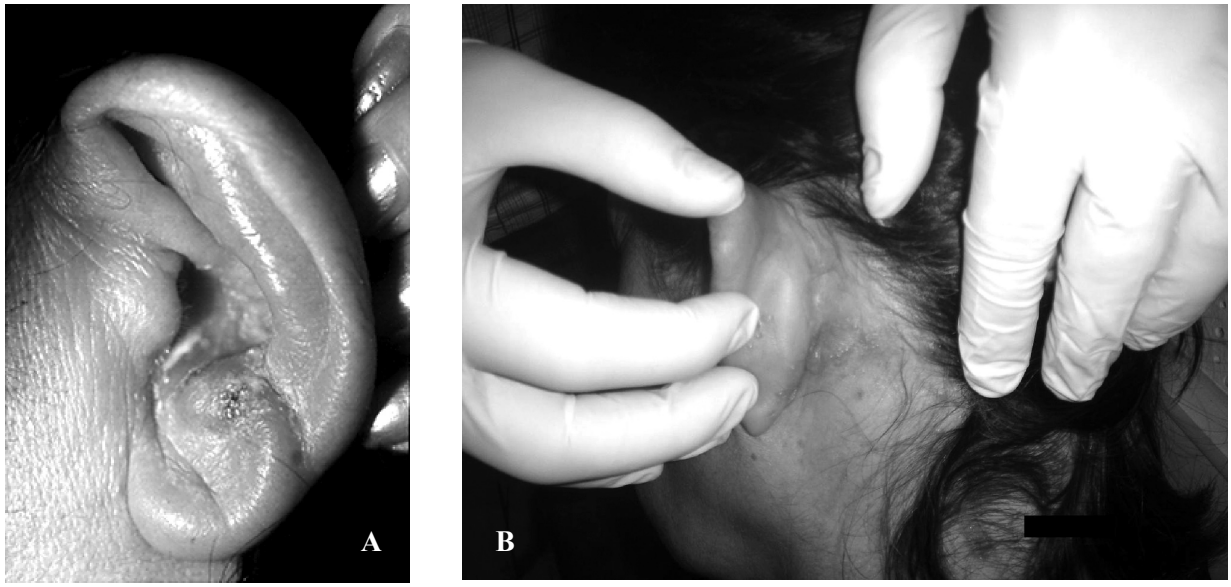

Figure 1. Vesicles in RHS a) on the pinna b) on the mastoid and cervical region.

Table 4. Facial nerve function (House-Brackmann grading system) before and after treatment in the 4 treatment regimens.

	Before treatment				After treatment			
	n	III	IV	V	I	II	III	V
Acyclovir + steroids	12	4	1	7	4	5	2	1
Acyclovir + valaciclovir	1	1			1			
Acyclovir	1			1			1	
Steroids	1			1	1			
Total	15	5	1	9	6	5	3	1

cases although the degeneration exceeded the 90% the recovery was satisfactory (grade I and II).

DISCUSSION

In this study, 15 (10%) out of the 149 patients presenting with unilateral acute facial palsy suffered from RHS. This is consistent with the incidence reported in other studies[12,16,17], in which RHS cases ranged from 3.3% to 18% of patients with unilateral acute facial palsy. In the present study, the RHS cases in relation to Bell's (idiopathic) palsy cases were 9:1.

In 10 out of the 15 patients the vesicles were localized on the external ear. The first sign of RHS may initially be presented as erythema of the auricle[18] or as vesicles on the external ear. When the vesicles become apparent after the facial paralysis then the facial paresis (or paralysis) may be misdiagnosed as Bell's palsy. There is also a clinical condition not included in the present study called «zoster sine herpete», which is characterized by facial paralysis in the absence of vesicles; the condition is diagnosed based on a four-fold rise in serum antibody titre to VZV[19].

The distribution of major symptoms of RHS is shown in Table 3. The vestibular symptoms dominated over all the other symptoms. In other studies, vertigo has been reported to be a more frequent symptom and occurs in a significant number of patients with RHS, from 72%[20] to 85%[21]. It was shown that in RHS both the superior and the inferior division of the vestibular nerve are affected[22]. Although hearing loss incidence in RHS was reported to be high (85% of cases[21]), in the present study it occurred in only 26% of the cases. The hearing loss is always of sensorineural type[16].

Seventh and eighth cranial nerve dysfunction in RHS is considered to be caused primarily by VZV neuritis; secondarily by inflammatory oedema of these nerves in their course within the temporal bone[1,6]. The

Table 5. Relation between electroneurography (ENoG) and nerve excitability test (NET) results and degree of recovery of facial nerve function in RHS.

	Satisfactory	Non-satisfactory
ENoG <90% + normal NET	5 (cases)	-
ENoG <90% + diminished NET	2	-
ENoG <90% + no response in NET	-	1
ENoG >90% + normal NET	4	-
ENoG >90% + no response in NET	-	3
Total	11	4

nerve oedema in the confined space within the facial canal or internal auditory meatus induces nerve compression and hypoxia, leading to further degeneration of the nerves. Inflammation and oedema of the paralyzed facial nerve in the Fallopian canal have been demonstrated during decompression surgery in patients with RHS[23].

The antiviral agent acyclovir is a nucleotide analogue that interferes with herpes virus DNA polymerase and inhibits DNA replication, preventing further proliferation or spread of VZV. Moreover, the antiedematous effect of steroids is clinically well confirmed. Thus, the combined therapy with acyclovir-steroids is expected to eliminate the oedema, to avoid immunological reactions, and to reduce proliferative formations[24].

It has been shown[11,16] that if RHS was not treated, the recovery rate to normal facial function was very low between 21% and 31% respectively, demonstrating the poor natural outcome of the disease. In our study, the therapeutical benefit of the treatment for RHS was proved as the recovery rate after treatment was 73%. In other studies, the recovery rate to grade I and II especially after the combined therapy of acyclovir with steroids was reported to range from 80 to 85%[13,25-27]. However, in Ko's study[12] the recovery rate was 53%.

Murakami et al[26] supported the effectiveness of early treatment in RHS in a sample of 80 patients; they found that if the treatment (prednisone and acyclovir) initiated within 3 days of the onset of the disease the patients significantly improved, compared to the cases in which the treatment was delayed for more than 3 days after the onset. In the same study, it was demonstrated that there was no significant difference in facial nerve outcome between intravenous and oral acyclovir treatment.

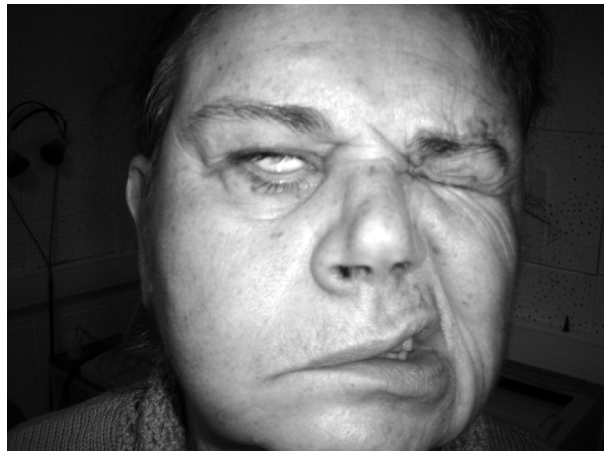

Figure 2. Non-satisfactory recovery 6 months after the onset of RHS (grade V according to House-Brackmann system).

The beneficial effect of the combined treatment of acyclovir with steroids compared to steroids alone was shown in Kinishi et al's[27] study in which the former treatment resulted in complete recovery to grade I in 90% of cases and in the latter in 64% of cases. Inamura et al[28] reported no beneficial effect on facial function when only acyclovir was administered in RHS.

According to our results (Table 5), it seems that the NET predicted better the final recovery than the ENoG. It is possible that the nerve degeneration was better determined after a minimal applied electrical stimulation (NET) compared to a maximal stimulation (ENoG). Thus, a normal or diminished response on NET was in favor of good prognosis and a lack of response on NET could predict a poor recovery. In a recent study, Ikeda et al[29] advocated that in Bell's

palsy, RHS and zoster sine herpete, the NET response was an especially important prognostic factor of facial paralysis; in the same study[29], it was also shown that the poor recovery rate was only 3% in patients who were normal on NET, and the poor recovery rate increased to 83% when the NET response was absent. In agreement with our results, it was concluded[29] that an abnormal response on NET was considered to be a high risk factor for the poor prognosis of facial paralysis.

In conclusion, a significant number of RHS cases may accompanied by cochleovestibular symptoms and in particular vertigo and balance disorder. Instead of the low recovery rate reported for the natural course of RHS[11,16], the combined treatment of acyclovir with steroids resulted in satisfactory recovery in 75% of patients. Among the electrophysiological tests, the NET was demonstrated to be the most useful method in the prognostication of RHS.

Το σύνδρομο Ramsay Hunt: Κλινική ανάλυση 15 περιστατικών

Γεώργιος Ψύλλας, Γιάννης Κωνσταντινίδης, Βίκτωρ Βιτάλ, Μιλτιάδης Τσαλιγόπουλος

Α΄ Πανεπιστημιακή ΩΡΛ Κλινική Νοσοκομείου ΑΧΕΠΑ, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης

ΠΕΡΙΛΗΨΗ: Το σύνδρομο Ramsay Hunt (RHS) χαρακτηρίζεται από περιφερική πάρεση ή παράλυση του προσωπικού νεύρου σε συνδυασμό με την εμφάνιση φυσαλιδώδους εξανθήματος στο έξω αυτί.

Υλικό-Μέθοδοι: Αξιολογήθηκαν 15 ασθενείς που έπασχαν από RHS. Σε όλους τους ασθενείς έγινε λήψη ιστορικού, κλινική εξέταση και στη συνέχεια υποβλήθηκαν σε αγωγή με στεροειδή και ακυκλοβίρη. Για την εκτίμηση της λειτουργίας του προσωπικού νεύρου χρησιμοποιήθηκε το σύστημα ταξινόμησης κατά House-Brackmann (HB I-VI) καθώς και οι ηλεκτροφυσιολογικές εξετάσεις της δοκιμασίας ερεθιστότητας (NET) και ηλεκτρονευρονογραφίας.

Αποτελέσματα: Στο RHS, τα πιο συχνά συνοδά συμπτώματα ήταν από το αιθουσοκοχλιακό σύστημα (73%) και κυρίως η εμφάνιση ιλίγγου και διαταραχής της ισορροπίας. Η συνδυασμένη θεραπεία της ακυκλοβίρης και των στεροειδών είχε ως αποτέλεσμα την μεγάλη βελτίωση της λειτουργίας του προσωπικού νεύρου στο 75% των περιπτώσεων. Η ανάνηψη ήταν σε όλες τις περιπτώσεις ανάλογη των αποτελεσμάτων του NET. Η εξέλιξη της παράλυσης δεν ήταν ικανοποιητική σε τέσσερις περιπτώσεις στις οποίες το NET ήταν καταργημένο.

Συμπέρασμα: Στο RHS είναι πιθανόν να λαμβάνουν χώρα νευρίτιδα και οίδημα μέσα στον έσω ακουστικό πόρο, τα οποία προκαλούν πάρεση ή παράλυση του προσωπικού νεύρου και συμπτώματα από το αιθουσοκοχλιακό σύστημα. Γι' αυτόν το λόγο, για την θεραπευτική αντιμετώπιση του RHS συνιστάται η συνδυασμένη αγωγή των αποιδηματικών στεροειδών με την αντιική ακυκλοβίρη. Η εξέταση με το NET είναι η πιο ενδεδειγμένη ως προγνωστική μέθοδος γι' αυτό το σύνδρομο.

Λέξεις Κλειδιά: Σύνδρομο Ramsay Hunt, Ωτικός έρπης ζωστήρας, Παράλυση προσωπικού νεύρου, Ακυκλοβίρη, Στεροειδή.

REFERENCES

1. Hunt JR. On herpetic inflammations of the geniculate ganglion, a new syndrome and its complication. J Nerv Ment Dis 1907;34:73-96.
2. Furuta Y, Takasu T, Suzuki S, Fukuda S, Inuyama Y, Nagashima K. Detection of latent varicella-zoster virus infection in human vestibular and spiral ganglia. J Med Virol 1997;51:214-6.
3. Gershon AA, Takahashi M, Seward J. Varicella vaccine. In Plotkin SA, Orenstein WA, eds. Vaccines. 4th ed. Philadelphia: WB Saunders Co, 2004:783-823.
4. Nardone A, de Ory F, Carton M, Cohen D, van Damme P, Davidkin I, et al. The comparative sero-epidemiology of varicella zoster virus in 11 countries in the European region. Vaccine 2007;25:7866-72.
5. Aizawa H, Ohtani F, Furuta Y, Sawa H, Fukuda S. Variable patterns of varicella-zoster virus reactivation in Ramsay-Hunt syndrome. J Med Virol 2004;74: 355-60.
6. Furuta Y, Takasu T, Fukuda S, Sato-Matsumura KC, Inuyama Y, Hondo R, et al. Detection of varicella-zoster virus DNA in human geniculate ganglia by polymerase chain reaction. J Infect Dis 1992;166:1157-9.
7. Wackym PA. Molecular temporal bone pathology: II. Ramsay Hunt syndrome (herpes zoster oticus). Laryngoscope 1997;107:1165-75.
8. Jonsson L, Tien R, Engstrom M, Thomas KA. Gd-DTPA enhanced MRI in Bell's palsy and herpes zoster oticus: an overview and implications for future studies. Acta Otolaryngol (Stockh) 1995;115:577-84.
9. Brandle P, Sartoretti-Schefer S, Bohmer A, Wichmann W, Fisch U. Correlation of MRI, clinical and electroneuronographic findings in acute facial palsy. Am J Otol 1996;17:154-61.
10. Robillard RB, Hislinger RL Jr, Adour KK. Ramsay Hunt facial paralysis: clinical analyses of 185 patients. Otolaryngol Head Neck Surg 1986;95:292-7.
11. Devriese PP, Moesker WH. The natural history of facial paralysis in herpes zoster. Clin Otolaryngol Allied Sci 1988;13:289-98.
12. Ko JY, Sheen TS, Hsu MM. Herpes zoster oticus treated with acyclovir and prednisolone: clinical manifestations and analysis of prognostic factors. Clin Otolaryngol 2000;25:139-42.
13. Yeo SW, Lee DH, Jun BC, Chang KH, Park YS. Analysis of prognostic factors in Bell's palsy and Ramsay Hunt syndrome. Auris Nasus Larynx 2007;34:159-64.
14. Psillas G, Constantinidis J, Printza A, Vital V. [Estimating the prognosis of peripheral facial paralysis: Is the minimal nerve excitability test still up to date?]. HNO 2007;55:625-9.
15. Fisch U. Prognostic value of electrical tests in acute facial paralysis. Am J Otol 1984;5:494-8.
16. Peitersen E. Bell's palsy: The spontaneous course of 2,500 peripheral facial nerve palsies of different etiologies. Acta Otolaryngol 2002(suppl);549:4-30.
17. Sweeney CJ. Ramsay Hunt syndrome. J Neurol Neurosurg Psychiatry 2001;71:149-54.
18. Adour KK. Otological complications of herpes zoster. Ann Neurol 1994;35:S62-S64.
19. Murakami S, Honda N, Mizobuchi M, Nakashiro Y, Hato N, Gyo K. Rapid diagnosis of varicella zoster virus infection in acute facial palsy. Neurology 1998;51:1202-5.
20. Devriese PP. Facial paralysis in cephalic herpes zoster. Ann Otol Rhinol Laryngol 1968;77:1101-19.
21. Abramovich S, Prasher DK. Electrocochleography and brain-stem potentials in Ramsay Hunt syndrome. Arch Otolaryngol Head Neck Surg 1986;112:925-8.
22. Lu YC, Young YH. Vertigo from herpes zoster oticus: superior or inferior vestibular nerve origin? Laryngoscope 2003;113:307-11.
23. Honda N, Yanagihara N, Hato N, Kisaki H, Murakami S, Gyo K. Swelling of the intratemporal facial nerve in Ramsay Hunt syndrome. Acta Otolaryngol 2002;122:348-52.
24. Stennert E. Pathomechanisms in cell metabolism: a key to treatment of Bell's palsy. Ann Otol Rhinol Laryngol 1981;90:577-80.
25. Uri N, Greenberg E, Kitzes-Cohen R, Doweck I. Acyclovir in the treatment of Ramsay-Hunt syndrome. Otolaryngol Head Neck Surg 2003;129:379-81.
26. Murakami S, Hato N, Horiuchi J, Honda N, Gyo K, Yanagihara N. Treatment of Ramsay Hunt syndrome with acyclovir-prednisone: significance of early diagnosis and treatment. Ann Neurol 1997;41:353-7.
27. Kinishi M, Amatsu M, Mohri M, Saito M, Hasegawa T, Hasegawa S. Acyclovir improves recovery rate of facial nerve palsy in Ramsay Hunt syndrome. Auris Nasus Larynx 2001;28:223-6.
28. Inamura H, Aoyagi M, Tojima H, Koike Y. Effects of acyclovir in Ramsay Hunt syndrome. Acta Otolaryngol 1988;446:111-3.
29. Ikeda M, Abiko Y, Kukimoto N, Omori H, Nakazato H, Ikeda K. Clinical factors that influence the prognosis of facial nerve paralysis and the magnitudes of influence. Laryngoscope 2005;115:855-60.