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Ramsay Hunt syndrome: clinical presentation and prognostic factors

G. Psillas, S. Dova, F. Ieridou, A. Kyrgidis, J. Constantinidis

Department of Otorhinolaryngology and Head & Neck Surgery, AHEPA Hospital, Thessaloniki, Greece

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Abstract. *Objective*: Ramsay Hunt Syndrome (RHS) is a peripheral facial nerve palsy (FP) associated with otalgia and vesicular eruptions on the external ear. This study aimed to evaluate the clinical features of RHS and determine the prognostic factors.
Materials and methods: This was a retrospective study, which included 52 patients with RHS who underwent combined steroid and antiviral treatment. The House-Brackmann (HB) grading system was used for the initial presentation and final outcome, as follows: full recovery (HB I), satisfactory outcome (HB II), and poor recovery (HB V and VI). The associated clinical symptoms, side of FP, delay of treatment, time of initial facial function improvement, comorbid diseases, time of vesicle eruption, audiogram testing, initial nerve excitability test (NET), and electroneurography (ENoG) were evaluated to identify correlations with the final HB grade.
Results: At presentation, more than half (55%) the RHS patients were HB V and VI. Full recovery was achieved in 19 (36.5%) patients, there was a satisfactory outcome in 23 (44.2%), and poor recovery in 2 (3.8%). The most common symptoms were headache of the temporal area (57.6%) and imbalance (44.2%). The initial NET threshold and percentage degeneration on ENoG most significantly correlated with the final HB grade.
Conclusions: Headache in the temporal area and imbalance were the most common symptoms of RHS; while, the NET and ENoG were the most important prognostic factors. In the early phase, a lack of response on the NET and an increased percentage of degeneration on ENoG were clinically correlated with poor outcome.

Introduction

In 1907, Ramsay Hunt syndrome (RHS) was first described by James Ramsay Hunt.[1] About 12% of cases of peripheral facial palsy (FP) are associated with RHS, which is characterized by acute FP, otalgia, and the presence of erythematous vesicular rashes in the external auditory canal and pinna.[1,2] The RHS should be distinguished from RHS sine herpete, which can occur without ear rush,[3] and from herpes zoster oticus, which presents without FP.[4] Occasionally, RHS can be accompanied by other cranial nerve dysfunctions, such as cochleovestibular symptoms, dysgeusia, or facial numbness.[2]

Following the primary infection, the varicella-zoster virus (VZV) becomes latent in the cells of the dorsal root ganglia and may be reactivated after a period of several decades; the otic involvement occurs in the geniculate, auditory, and vestibular ganglia.[5] There are several risk factors that can contribute to VZV reactivation, such as upper respiratory tract infection, emotional stress, aging, smoking, diabetes, depression, cancer, immuno-suppressive therapy, and chronic renal failure.[3,6]

The aim of this study was to investigate the clinical manifestations of RHS in order to better achieve an accurate diagnosis and initiate the appropriate treatment. In addition, we analyzed statistically significant correlations between clinical data and the level of final facial function to determine prognostic factors for patients.

Materials and methods

We retrospectively reviewed the clinical data of 52 patients diagnosed with RHS in our center between 2012 and 2017. The House-Brackmann (HB) grading system was used to evaluate the initial presentation, the time of improvement, and the final facial function. The recovery of facial function was categorized as: full recovery with HB I, satisfactory outcome with HB II, and poor recovery with HB V to VI. The extent of herpetic vesicles on the pinna, external ear canal, face, oral cavity, lips, or cervical region were also recorded, as well as the time of vesicle eruption before (or the same day) and after the FP onset. The following clinical data were analyzed statistically to identify correlations with the final HB grade: clinical symptoms including

imbalance or instability, headache in the temporal area, excessive lacrimation, dysgeusia, hyperacusis, and numbness in the head, face (lips, cheek), and tongue; individual characteristics, such as gender, age, side of FP, delay of treatment, and time of initial facial function improvement; and common comorbid diseases associated with RHS, such as diabetes mellitus, hypertension, or cardiovascular diseases.

A pure-tone audiogram (GSI-61 audiometer) was performed and video Frenzel goggles were used for all the patients to detect sensorineural hearing loss and spontaneous nystagmus, respectively; the outcomes were also evaluated to identify statistically significant correlations with the final HB grade. Finally, the nerve excitability test (NET) and electroneurography (ENoG) were included in the same statistical analysis to electrophysiologically evaluate the FP in the first 10 days after onset. However, three patients were admitted to our hospital between the 13th and 16th day; thus, the NET and ENoG were performed in these patients on the day of admission.

The Myoton 2 Facial Nerve Stimulator was used for the NET examination.[7] The test was initially performed on the healthy side and then on the affected side. The current intensity level at which a barely visible muscle twitch occurred as well as the NET threshold were used on both sides. The NET thresholds were compared between the two sides. A difference of 3.5 mA was defined as "normal"; a difference ≥ 3.5 mA was defined as "diminished"; and "no response" was defined as no facial reaction produced.

For the 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.[7] The applied current intensity was increased from zero to a maximal level sufficient to evoke the myogenic compound action potential (MCAP). The percentage of degenerated nerve fibers was calculated by dividing the amplitude of the MCAP of the affected side by that of the normal side.

The same therapy protocol was administered in all our patients affected by RHS as soon as they visited our hospital after the FP onset. This consisted of intravenous steroid (dexamethasone-iv 8 mg, 3 times daily) for 10 days followed by oral steroid (Solu-Medrol-per os 16 mg) for 5 days, with both having a tapering dose schedule. This was combined with oral antiviral Acyclovir for one week (800 mg, five times daily). The patients who did not have a full recovery were followed up for more than one year.

Statistical analysis

Scale variables were checked for normality. The Pearson $\chi 2$ or Fisher's exact tests were used for qualitative variables. Absolute and relative frequencies were obtained for demographic and clinical variables. To analyze factors influencing the HB response to treatment, Spearman's rho coefficient was used to highlight significant correlations, which were subsequently quantified via univariate and multivariate linear regression. The effect of each independent variable on the variance of the dependent was quantified and presented as an equation. The alpha level was set at 0.05. Statistical analyses were performed using the IBM SPSS 23.0 package (IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY: IBM Corp).

Results

The demographic and clinical characteristics of RHS patients are shown in Table 1. At presentation, more than half (55%) the RHS patients had severe HB grade V and VI. Full recovery was achieved in 19 (36.5%) patients, a satisfactory outcome in 23 (44.2%) patients, and poor recovery was noted in 2 (3.8%) patients. Facial nerve recovery was noticeable after a mean of 27.1 ± 19.8 days after the onset of palsy. Among the prognostic factors, the NET threshold (rho=0.639, $p<0.001$) and the percentage degeneration on the ENoG (rho=0.665, $p<0.001$) were significantly correlated with the final HB grade. For the ENoG, each percent increase was associated with 0.2% reduced odds for HB I (OR=0.002, 95% CI: 0,000-0,172, p=0.006). The estimated sensitivity and specificity of using the NET threshold to predict recovery was 92.5% and 80%, respectively; for the ENoG results, the estimated sensitivity and specificity were 59.3% and 100%, respectively. The final HB grade did not correlate with the following factors: gender, age, affected side of the facial nerve, delay of treatment, time of initial facial function improvement, time of vesicle eruption, and audiogram testing (Table 1). Of the clinical symptoms, headaches in the temporal region and FP affecting the ipsilateral

Table 1

Statistical correlations between characteristics of patients with Ramsay-Hunt syndrome (RHS) and the final House-Brackmann (HB) grade

Characteristics	Patients with RHS (%) N=52	Spearman's rho (*P*-value)
Sex		0.168 (0.233)
Male	26 (50)	
Female	26 (50)	
Age (y)	17 - 83	-.004 (0.977)
Mean ± SD	54.6 ± 18.9	
Affected side (right / left)	26 (50) / 26 (50)	0.250 (0.860)
HB grade	Initial Final	
I	- 19 (36.5)	
II	1 (1.9) 23 (44.2)	
III	20 (38.4) 5 (9.6)	
IV	2 (3.8) 3 (5.7)	
V	12 (23) 1 (1.9)	
VI	17 (32.6) 1 (1.9)	
Treatment delay (d)	0 - 16	0.197 (0.161)
Mean ± SD	1.8 ± 3.7	
Initial improvement (d)	4 - 90	0.206 (0.165)
Mean ± SD	27.1 ± 19.8	
Vesicle eruption		
Before FP or same time (N=34) (mean ± SD)	0 – 10 d (2.7 ± 2.9)	0.101 (0.570)
After FP (N=18) (mean ± SD)	1 – 16 d (4.8 ± 4.5)	-.157 (0.535)
ENoG		0.665 (*<0.001*)
% degeneration	22 - 100	
Mean ± SD	73.4 ± 2.7	
NET threshold		0.639 (*<0.001*)
Normal	33 (63.4)	
Diminished	6 (11.5)	
No response	11 (21.1)	
Symptoms		
Headache	30 (57.6)	-.025 (0.860)
Imbalance	23 (44.2)	0.165 (0.242)
Lacrimation	17 (32.6)	0.266 (0.057)
Dysgeusia	14 (26.9)	-.140 (0.323)
Numbness	9 (17.3)	0.144 (0.309)
Nystagmus (paralytic)	7 (13.4)	0.085 (0.505)
Hyperacusis	4 (7.6)	-.233 (0.097)
Audiometry testing (N=51)		0.139 (0.332)
Normal	37 (72.5)	
Sensorineural hearing loss	14 (27.4)	

FP: facial palsy, ENoG: electroneurography, NET: nerve excitability test

side occurred more frequently in RHS (57.6%); imbalance or instability was present in 23 (44.2%) patients; and paralytic, unidirectional nystagmus in 7 (13.4%) patients. Other symptoms, such as lacrimation, dysgeusia, hyperacusis, and numbness in the head, face (lips, check), and tongue were less frequent.

The common presentation areas of vesicles are shown in Table 2. Vesicles may erupt before (21 cases), after (18 cases), or at the same time (13 cases) as FP onset. In seven (13.4%) patients, the vesicles were located on more than one area of the face and ear. Five patients exhibited vesicles on the pinna and another area as follows: pinna and cervical area (two cases), pinna and oral region (one case), pinna and face (one case), or pinna, oral, cervical, and face (one case); while, two patients had vesicles on the mastoid and cervical area.

Table 2
Localization of herpetic vesicles in relation to the time of facial nerve palsy (FP).

	Before FP (N=21) or at the same time (n=13)	After FP	Total
Pinna	22	10	32 (61.5%)
External ear canal	6	5	11 (21.1%)
Lips	3	-	3 (5.7%)
Mastoid area	2	-	2 (3.8%)
Face	-	2	2 (3.8%)
Oral cavity	-	1	1 (1.9%)
Cervical region	1	-	1 (1.9%)
	34	18	52 patients

Sensorineural hearing loss occurred in 14 (14/51, 27.4%) patients. One patient failed to undergo audiometry testing; in six cases, the hearing loss was flat; in seven cases, hearing was restricted at high frequencies; and unilateral cophosis was revealed in one case. Magnetic resonance imaging was effectuated in one third (17 cases) of the patients and an enhancement of the intracanalicular segment of the facial nerve was detected in one case. Fifteen (28.8%) RHS patients had other comorbidities such as diabetes mellitus (type I in one case, type II in three cases), hypertension (four patients), hypothyroidism (two cases), cardiovascular diseases (arrhythmia in two patients, coronary disease in one patient), and infectious diseases (AIDS in one case, hepatitis C in one case).

Multiple linear regression analysis of facial nerve recovery was performed and the prognostic factors that were statistically significantly correlated during univariate analysis were included. The final model was the following: HB = 0.883 + 0.517 * NET + 1.335 * ENoG. The NET threshold was the sole variable that statistically significantly influenced the final HB result (p=0.033) as the ENoG results became non-significant (p=0.090) when adjusted for the effect of the NET threshold. Initial clinical improvement was also included in a sensitivity analysis because it was proposed as a relevant variable and the equation was: HB = 0.946 + 0.565 * NET + 1.358 * ENoG - 0.04 * initial improvement in days.

Discussion

Studies have shown that the recovery rate in RHS is worse than in Bell's palsy[8-10] and only 30% of RHS patients had a full recovery without any treatment.[11] However, the combination of steroid and antiviral treatment has improved recovery rates in RHS patients, ranging from 61.1% to 100% of cases.[3] In our study, although more than half the patients (55.6%) had initially severe FP, a good prognosis (final HB I and II) was noted in 80.7% of patients after steroid and antiviral treatment. From a recent review of literature,[3] full recovery was achieved in 33.3%-81.1% of RHS patients and a satisfactory outcome in 3.6% - 36.3%, and this corroborated our results.

The RHS has been described as a cranial polyneuropathy disease caused by VZV that involves cranial nerves, such as V, VII, VIII, IX, X, and XII.[2] In our patients, headache was the most common symptom, especially in the temporal area. The typical pain of acute herpes zoster affecting the head region, even during the pre-eruptive period (lasting about 3 days), has been well described[12] as stabbing (sharp, electrical shock-like), moderate to severe, and often awakening patients from sleep. It is located unilaterally, spreading in 20% of cases to the temporal, frontal or occipital zones.

Usually, vesicles appear along specific dermatomes, depending on the sensory afferent fibers that correspond to the pain origin area. Devriese and Moesker[11] reported that in most cases the vesicle eruption and FP appeared concurrently and facial recovery was better when the vesicles preceded the FP. In most of our patients, the vesicles erupted before the FP (Table 2), especially on the pinna and the time of eruption did not affect the prognosis (Table 1).

Vestibulocochlear symptoms such as imbalance, vertigo, hearing loss, and tinnitus are commonly associated with RHS[1] due to the close proximity of the geniculate ganglion to the VIII cranial nerve within the bony facial canal. Some authors found

a statistically significant relation between the vestibular disturbance (sensorineural hearing loss) and the severity of FP and a poor prognosis;[13,14] while in others studies, this correlation is not evident,[15] similar to our results (Table 1). More specifically, twenty-three (44.2%) of our patients complained of imbalance, in comparison to 32%[15] and 37%[4] in previous studies. However, nystagmus (direction-fixed, paralytic) was found in only 30% (7/23) of our RHS cases suffering from imbalance compared with 61% in the study by Kim et al.[16] Pathophysiologically, the VZV might spread directly from the geniculate ganglion and VII nerve to the VIII nerve into the internal auditory canal through the vestibule-facial anastomosis.[13] The lesion sites responsible for vestibular dysfunction remain unclear, but possibly include the vestibular nerve and/or labyrinth, and the superior vestibular nerve and/or inferior vestibular nerve.[17] Fourteen (27.4%) of our patients had sensorineural hearing loss, in contrast to 50%,[15] 63%,[13] and 76%[4] in other studies. In half (7/14) of our patients, the sensorineural hearing loss was restricted to high frequencies, in agreement with other studies.[4,13] It has been reported that a VZV spread from the internal auditory canal to the cochlea through cerebrospinal fluid and perilymphatic fluid could result in basal turn damage earlier than apical turn damage.[4]

Multiple regression analysis of FP improvement showed that the NET threshold and percentage degeneration on ENoG were the most important factors for predicting the prognosis of FP patients. A normal or diminished response on the NET was favored a good prognosis and a lack of response could predict poor recovery. In Ikeda's study,[8] the predictive prognostic value of the NET for Bell's palsy was underlined, as the poor recovery rate was 3% in patients with a normal NET and 83% when the NET response was absent; Ikeda et al.[8] concluded that an abnormal response on the NET was a high risk factor for a poor prognosis of FP. Similarly, Kasse et al[18] demonstrated that patients with FP who initially had no response on the NET presented with a higher incidence of an unfavorable final HB grade.

The ENoG is an objective electrophysiologic measurement of the MCAP used to assess nerve degeneration. According to our data, an increased percentage degeneration on the ENoG was associated with a poorer recovery to HB I or II. Fisch[19] stated that MCAP degeneration reaching 95% within 2 weeks gave a 50% chance of a poor recovery. The ENoG is performed at least 3 days after the FP onset, because it is the appropriate time for Wallerian degeneration to propagate from the intratemporal site of the lesion to the portion distal to the stylomastoid foramen, the region where electrical ENoG stimulation occurs.[10] The ENoG has already been reported to statistically correlate with prognosis in RHS.[10,20,21] Moreover, comparatives studies[20,21] revealed that MCAP degeneration was significantly higher in patients with RHS than Bell's palsy, indicating that damage to the facial nerve was more important in RHS than Bell's palsy.

According to several studies,[9,22] the best therapeutic results were achieved when the treatment was initiated as early as possibly, even before the third day of RHS onset. Coulson et al.[15] concluded that the combination of an antiviral with a steroid, with the steroid given 5 days after the first RHS symptoms, was the most effective treatment. This study suggested[15] that the anti-inflammatory action of steroids was important at the time of greatest inflammation to achieve the best efficacy. However, our results (Table 1) corroborated the Yeo et al. study[14] data and did not demonstrate any significant relationship between the onset of treatment and the prognosis for RHS.

Conclusion

In conclusion, patients with RHS had a relatively high recovery rate for facial function (80.7%) after a combination of steroid and antiviral treatment. A headache in the temporal area and imbalance were relatively common in RHS. Almost half the RHS patients suffered from cochleovestibular symptoms, such as imbalance and sensorineural hearing loss, especially at high frequencies. The NET threshold and the percentage degeneration on the ENoG were the most important prognostic indicators for predicting the final HB grade in RHS patients. In the early phase, a lack of response on the NET and an increased percentage of degeneration on the ENoG predicted a poor outcome.

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Dr George Psillas
Department of Otorhinolaryngology and Head & Neck Surgery,
AHEPA Hospital,
1, Stilponos Kyriakidi St.,
GR 546 36 Thessaloniki, Greece
Tel.: +30-2310-994-762
Fax +30-2310-994-916
E-mail: psill@otenet.gr