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Original Article

Typical or Atypical Ramsay–Hunt Syndrome in Delayed Facial Palsy After Stapedectomy?

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OBJECTIVES: The aim of this study was to define the typical pattern for varicella zoster virus (VZV) reactivation in delayed facial palsy (DFP) after stapedectomy for otosclerosis.

MATERIALS and METHODS: Review of the relevant literature, personal casistics, and case-report

RESULTS: In total, 48 cases of DFP after stapes surgery have been described so far, including the reported case with exclusive manifestation of atypical Ramsay Hunt syndrome (RH); in the personal series of 1253 stapedectomies, DFP occurred in only one case (0.08%). Complete DFP (House–Brackmann grade VI) rapidly developed 12 days after surgery; RH appeared 2 days later, confirming the role of VZV. The DFP started improving after 8 weeks and completely recovered 6 months later.

CONCLUSION: Acute otalgia prior to DFP should raise the suspicion of VZV reactivation. Atypical RH is the most frequent pattern that occurs in DFP after stapedectomy.

KEYWORDS: Ramsay Hunt syndrome, zoster sine herpete, delayed facial palsy, stapedotomy, varicella zoster virus

INTRODUCTION

Delayed facial palsy (DFP) is an uncommon complication after middle ear surgery; it occurs after >72 hours of an uneventful ear surgery [1]. Shea described this phenomenon as "five and a half day syndrome," meaning that all his personal observations shared the same time lag from surgery. [2] DFP after stapedectomy is a very rare event (0.22%) [3]. Its incidence in the literature ranges between 0.07% and 1.4%. [4-6] While immediate facial palsy is easily explained by the use of local anesthetics (if transient) or by intraoperative severe surgical trauma (if permanent), many hypotheses have been proposed about the late facial nerve dysfunctions, including reactivation of a quiescent virus colonizing the nerve ganglion. According to Shea et al. [4] the most probable etio-pathogenetic mechanism for DFP is the activation of a latent herpesvirus in the geniculate ganglion, induced by mechanical stimulation or reactive inflammation of the facial nerve during middle ear surgery. This hypothesis has been supported by many other observations after otological surgical procedures [7-18] and preventive antiviral therapy has been proposed in patients with positive history to varicella zoster virus and herpes simplex virus 1 and 2. However, serological search of a viral etiology is often inconclusive, not always identifying which virus (HSV type 1, 2, or VZV) is involved; the proposed use of preventive therapy with antivirals in all stapedectomy patients is still debated and often not applied in clinical practice [4-7].

The purpose of this work is to review the relevant literature on DFP after stapedectomy, aiming at properly assessing the viral etiology and at identifying factors that might influence the prognosis or the recovery time or the choice of therapies, and describe a very unusual case of DFP characterized by VZV reactivation showed by the eruption of typical RH lesions.

MATERIALS and METHODS

A PubMed search encompassing all publications over the last 40 years was initially performed searching for "facial palsy OR paralysis OR paresis" AND "stapedectomy OR stapedotomy OR stapes surgery" using Boolean combinations; Further, the terms "delayed OR late" were added to the search. The date of last search was 18th March 2018. After screening all the articles abstracts, full-text works pertinent

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to DFP after stapedectomy were retrieved and analytically reviewed. Another PubMed search was conducted by searching for the "revision" stapes surgery utilizing the same Boolean combinations: the resulting abstracts were screened for relevance to account for all published cases of DFP. Chronology of onset and remission of the postoperative facial palsies, operated side, age and sex of patients, predisposing factors, surgical technique and tools, intraoperative observations, serological assays, pharmacological therapies, and facial outcomes were looked for in each article and tabulated on a Microsoft Excel spreadsheet. The heterogeneity of case-reports data set and case-series data set did not allow performing a pooled extraction analysis or meta-analysis regarding the effects of surgical procedures and DFP postoperative treatment. No language restrictions were applied and systematic review of the literature has been summarized. In addition to the literature search, a case of DFP with unique features of VZV infection in an adult who had undergone stapedectomy is described and the findings are compared with similar reports in scientific publications. The House–Brackmann (H-B) facial nerve grading system (1985) was used to evaluate the facial function in patients with DFP after stapedectomy and at the end of the recovery period [19].

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation (IRB 2016) and with the Helsinki Declaration of 1975, as revised in 2008. The patient has given written consent for publication.

Statistical Analysis

Descriptive statistical analysis was performed using Statistical Packages for the Social Sciences (SPSS) software for Mac version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Till date, 48 cases of DFP after stapes surgery have been described in the literature, including the present case; 33 of them occurred after stapedectomy and 14 after laser stapedoplasty. DFP were evenly distributed across age and sex and usually develops rapidly into complete palsy after few hours of onset. (Table 1) In all reported cases, the stapes surgeries were uneventful. In the literature, the onset time of DFP varies from 4 to 20 days after surgery (8.5±3.5 days). Interestingly, no specific macroscopic or otomicroscopic signs are usually observed neither reported in cases series; conversely, typical RH is characterized by the typical appearance of VZV vesicles in the conchal area and at the entrance of the external auditory meatus, facial palsy, hearing loss, and intense pain [25]. The association of increased anti-HSV 1-2 and VZV IgM with typical RH syndrome with ear pain and presence of vesicles at the entrance of the ear canal represent the most reliable indicators of VZV reactivation [29, 30]. However, after uncomplicated stapedectomy reported in the literature, typical RH was also absent in patients whose serologic tests proved positive. The recovery time after DFP onset ranges from 2 to 270 days (mean 45±43 days) with I-II final H-B grade in all the reported cases, regardless of the therapies.

A retrospective review of all subsequent operated patients during the last decade has been currently obtained for the purpose of this study. In our casistics, 1253 stapedectomies were personally performed by the same operator between January 1992 and May 2016, using the same conventional technique of footplate fenestration (0.4 to 0.6 mm calibrated hole) with a microdrill without connective tissue interposition. In the entire personal series, DFP occurred only in one patient, accounting for an incidence of 0.08%.

This patient was a 51-year-old female, admitted for bilateral otosclerosis, who underwent right stapedotomy under local anesthesia and interposition of a standard platinum-fluoroplastic piston (Audio Technologies, Piacenza, Italy) measuring 0.6 × 4.5 mm through a 0.7 mm platinotomy hole obtained using a microdrill. Preoperative pure tone audiometry showed bilateral up-sloping conductive hearing loss with a pure tone average of 58.7 dB HL in the right ear and 48.6 in the left; the mean air-bone gap (ABG) was 40 dB HL and 35.2 dB HL respectively. The middle ear anatomy was normal; in particular, the Fallopian canal was intact. Chorda tympani nerve was not stretched neither manipulated; no intraoperative complications were encountered.

The postoperative course was uneventful, except for slight dizziness induced by head movements during the first 12 hours. She was discharged on the 1st postoperative day with prescription of 400 mg oral cefixime q.i.d. and local instillation ear drops (0.3% ofloxacin solution b.i.d.) for 5 days.

On the 12th postoperative day, the patient complained of intense pain in the right (operated) ear, which was only partially relieved by anti-inflammatory drugs. On the 15th day, she noticed facial paresis on the operated side. The paresis progressed to complete palsy (H-B grade VI) within 24 hours. Painful edema of the soft tissues of the outer ear canal was observed; the retroauricular skin was hyperemic.

The patient had a positive history for chickenpox during childhood; she reported suffering of herpes labialis, once adult, due to sporadic reactivation of HSV type 1 and 2, which has been serologically proven in an occasion of a viral bout a few years earlier. Two days after the onset of facial palsy, elevated levels of specific anti-VZV IgG and IgM were observed by ELISA assay and complement fixation test.

Small vesicles with typical VZV morphology [21] appeared two days after the onset of the palsy at the triangular fossa and on the medial surface of the tragus, extending to the conchal area and the external meatus during the next 48 hours (Figure 1).

Pharmacological treatment with acyclovir (800 mg oral administration, five times per day) was started on postoperative day 15 (at the onset of the paresis) and continued for 10 days; eardrops had already been discontinued one week earlier and were not reintroduced. The eardrum looked normalized at micro-otoscopy, except for residual mild hyperemia around the malleus handle and the pars flaccida; pure tone audiometry revealed significant improvement in the air-conducted hearing threshold with reduction of the ABG within 20 dB HL and no sensorineural deficits.

An electroneuronography (ENoG), obtained 6 days after the onset of the palsy, showed complete denervation and an 80% decrease in nerve conduction by nerve excitability test. An electromyographic (EMG) study of the facial musculature on the 24th day after the onset confirmed the absence of response to stimulation at the stylomastoid foramen.

Table 1. Systematic review of literature

Author	Journal	# of cases	Incidence	Age	Side	Onset time (days from surgery)	Type of surgery	Predisposing factors	Signs/symptoms
Althaus SR [3]	Laryngoscope, 1973	5	0.22% (5/2307)	71, F 30, M 69, F 47, M 42, M	R L R L R	11 9 8 13 5	microdrill revision microdrill stapedectomy+vein	CT sectioned CT sectioned no CT sectioned no	severe pain * Otitis media Pain * no no
Storss LA et al. [20]	Laryngoscope, 1983	1	0.2% (1/503)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Zohar Y et al. [21]	J Laryngol Otol 1985	1	n.s.	32, F	R	8	microdrill + vein	CT sectioned/surgical stress	Numbness, normal otoscopy
Shea JJ [2]	J Laryngol Otol, 1988	1	0.1%	n.s., F	n.s.	5,5	microdrill + vein	Immune response in the facial nerve	n.s.
Bonkowsky V et al. [8]	Ann Otol Rhinol Laryngol 1998	2 (out of 7)	0.11% (2/1800)	49, F 19, M	n.s. n.s.	7 2 and 1/2	microdrill + vein (5 were tympanoplasty)	no no	n.s. n.s.
Glasscock and Shambaugh [1]	Surgery of the ear, Saunders eds. 1990	2	<1%	n.s. 19, M	n.s. n.s.	<10 1/2	microdrill + vein	Edema of the Fallopian canal no	n.s. n.s.
Smith MC et al. [22]	J Laryngol Otol, 1990	6	0.5%	29, M 40, M 44, M 51, M 50, M 22, F	n.s. n.s. n.s. n.s. n.s. n.s.	10 4 7 4 6 4	microdrill revision	no no Exposed facial nerve no no Aberrant facial nerve	n.s. n.s. n.s. n.s. n.s. n.s.
Wiet RJ [23]	Otolaryngol Clin North America, 1993	1	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Ng and Maceri [11]	American Journal of Otology, 1999	2		54, F 52, M	R L	5 6	KTP laser	no	n.s.
Shea JJ & Ge X [4]	Otol Neurotol, 2001	11	0.51% (11/2152)	mean age 53 (31–71, 3 R (5F, 6M)	8L,	7 8 16 7 7 10 8 5 10 7 8	3 microdrill, 8 Argon laser (6/11 were revisions)	5 with dehiscent facial canal, 2 CT sectioned/stretched o manipulated, 1 granulomatous reaction to gelfoam, 1 fever blister, 1 sinusitis	
Marioni G. et al. [24]	ORL J Otorhinolaryngol Relat Spec, 2002	1	n.s.	59, M	R	7	microdrill	no	
Mills et al. [35]	Clin Otolaryngol Allied Sci, 2003	3	37.5% (3/8); 0%	47, M 42, F 44, M	L L L	16 10 11	KTP laser	n.s. n.s. n.s.	n.s. n.s. n.s.
Salvinelli F. et al. [5]	Am J Otolaryngol, 2004	7	1% (7/706)	61, F 54, F 61, F 37, F 45, M 40, F 36, F 23, F		10 11 10 9 8 5 9 20		no no no no no no no no	no no no no no no no no
Cohen M et al. [7]	Otol Neurotol, 2010	2	0.4% (2/450)	n.s. n.s.	R R	12 41	microdrill	n.s. n.s.	periauricular pain, dysgeusia
Révész P, et al. [6]	Case Reports in Medicine, 2014	2	1.3% (2/149)	52, F 42, M	R R	8 13	KTP laser	no no	Parageusia and pain, slight pain

* 3 days before DFP onset; n.s. = not specified; n.p.= not performed

Author	Positive history (recent labial HSV /previous VZV)	HSV -HZV serology	H-B grade at onset	Therapy	Recovery time (days)	Final H-B grade
Althaus SR [3]	n.s.	n.s.	Complete	Vasodilatators, steroids	49	I
	n.s.	Bacterial	Complete	Vasodilatators, antibiotics	28	I
	n.s.	n.s.	Complete	Nicotinic acid	120	I
	n.s.	n.s.	Incomplete	-	22	incomplete
	n.s.	n.s.	Complete	Steroids, vasodilators	56	I
Storss LA et al. [20]	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Zohar Y et al. [21]	n.s.	negative	Complete	Steroids (prednisolone)	30	I
Shea JJ [2]	n.s.	n.s.	complete	Steroids	quick	I
Bonkowsky V et al. [8]		5 HSV1 (IgM in 1) - 2 n.p.				
	n.s.	n.s.	n.s.	Steroid + acyclovir	n.s.	n.s.
	n.s.	n.s.	n.s.	Steroid + acyclovir	n.s.	n.s.
Glasscock and Shambaugh [1]	n.s.	n.s.	n.s.	Steroids	1 to several weeks	I
	n.s.	n.s.	n.s.	Steroid + acyclovir	n.s.	n.s.
Smith MC et al. [22]	n.s.	n.s.	Incomplete	Steroids	11	I
	n.s.	n.s.	Incomplete	-	11	I
	n.s.	n.s.	Incomplete	-	10	I
	n.s.	n.s.	Incomplete	-	2	I
	n.s.	n.s.	Incomplete	Steroids	3	I
	n.s.	n.s.	Incomplete	Steroids	36	I
Wiet RJ [23]	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Ng and Maceri [11]	n.s.	n.p.	VI	Steroids	90	I-II
			VI	Steroids	60	I-II
Shea JJ & Ge X [4]	1	HSV, VZV				
		n.s.	III		11	I
		HSV1-2 VZV	IV		26	I
		n.s.	III		31	II
		HSV1-2 VZV	III		18	I
		n.s.	V		69	I
		n.s.	IV		30	I
		HSV1-2 VZV	V	preventive acyclovir	49	II
		HSV1-2 VZV	III	avoided DFP in revision	18	I
		HSV1-2 VZV	III		77	I
		n.s.	III		51	I
		VZV	IV		30	I
Marioni G. et al. [24]			IV	Steroids (prednisone)	15	I
Mills et al. [35]	n.s.	n.s.	II	-	30	I
	n.s.	n.s.	IV	steroids	90	I
	n.s.	n.s.	II	-	60	I
Salvinelli F. et al. [5]	yes	HSV-1 IgM in 1 patient	II	acyclovir	30	I
	yes		III		30	I
	yes		II		30	I
	yes		III		55	II
	yes		III		270	I
	yes		IV		30	I
	yes		IV		30	I
	yes		IV		20	I
Cohen M et al. [7]	no	n.p.	VI	Steroids (prednisone)	86	I
	no	n.p	VI	and antiviral	>10	I
Révész P, et al. [6]		suspected virus	II	Steroids	36	I
		reactivation by heat	III	(methylprednisolone) and antiviral	43	I
				Steroids (medrol) and antiviral		

A surgical re-exploration of the middle ear was not deemed useful nor was the decompression of the Fallopian canal up to its labyrinthine segment through a combined approach, as proposed in the past by some authors [26].

Eight weeks later, the facial palsy gradually started to improve, and at six months, it had returned to H-B grade III. At that time, a control EMG showed a significant increase of active motor units of the VII nerve. The facial weakness further improved in the following 8

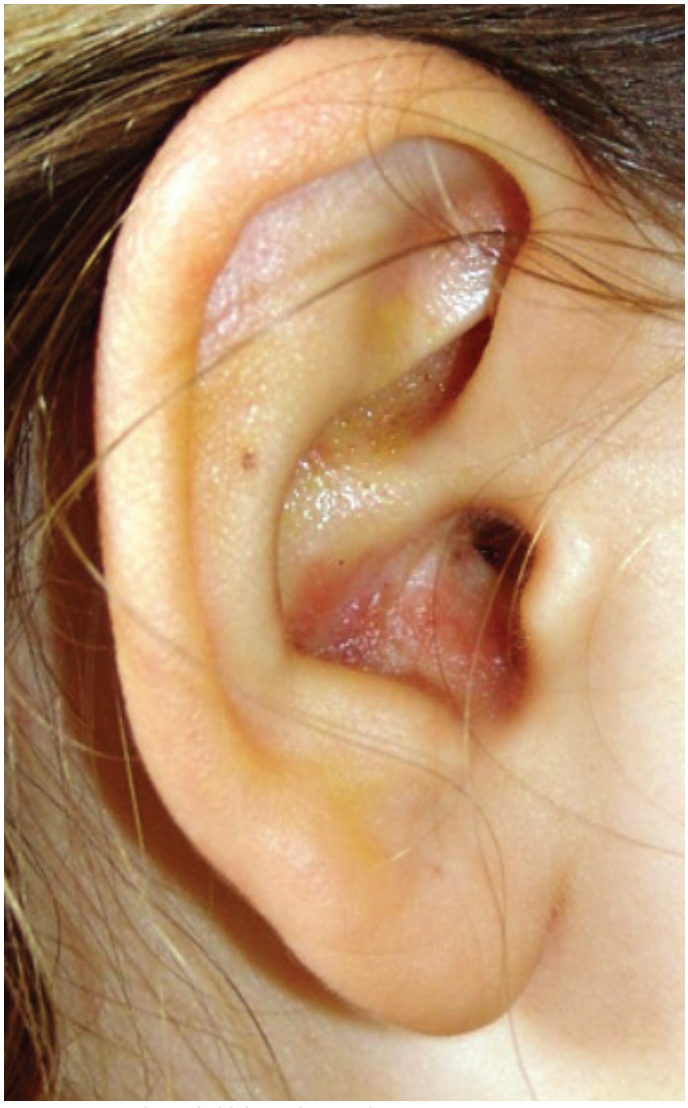

Figure 1. Typical vesicle blebs in the concha

months, when it reached grade II, then stabilized with minimal residual dynamic dysfunction and slight oculo-oral synkinesis.

DISCUSSION

Typical RH was first described by James Ramsay Hunt in 1907; [25] the viruses can be reactivated during periods of generic temporary depression of the immune system induced by physical or emotional stress, concurrent bacterial or viral infections, neoplasms, mechanical or surgical trauma, including local surgical stress. [26] In 1972, Steffen and Shelby [27] firstly described an "Atypical RH Syndrome," starting with vague symptoms and without the typical vesicular eruption in the concha ("Zoster sine herpete"). This clinical pattern is generally extremely rare but it might proceed with the involvement of other dermatomes or districts of the neck and face. [27-29] To our knowledge, this is the first case of DFP with typical RH syndrome after stapedectomy reported in the literature; the appearance of the pathognomonic herpetic vesicles within few days after the onset of the palsy allowed us to confirm unequivocally the pathogenetic role of VZV reactivation. In literature, RH with DFP has been reported only in two cases, both after acoustic neuroma surgery. [9, 10] In particular, Gianoli et al. [9] described a case of DFP with typical RH after trans-labyrinthine resection of an acoustic neuroma: the herpetiform lesions appeared on the ipsilateral ear canal and extended to the ipsilateral buccal mucosa; anti-VZV antibodies were elevated.

In DFP, an isolated increase in serum anti-VZV IgG antibodies has been reported in literature confirming the suspect a viral reactivation. [32, 4] However, because most patients with breakthrough VZV will have preexisting elevated IgG antibody titers to VZV, conventional IgG determinations are of limited value unless measurements are performed both during the acute and convalescent phase. Evidence of VZV-specific IgM in serum indicates recent exposure to VZV but does not discriminate between primary infection, reinfection, and reactivation. [33] Moreover, the absence of IgM antibody does not exclude a recent VZV exposure because IgM antibodies are inconsistently observed even among cases with PCR-confirmed infection by VZV and the most reliable and sensitive laboratory method for confirming varicella is the detection of VZV DNA in samples (vesicular swabs, scabs, and saliva) obtained from skin lesions using PCR. [33] Unfortunately, this examination is not possible in DFP cases because typical RH is absent and none has been reported data from saliva in the literature.

Furthermore, although the etiopathogenetic role of herpes virus reactivation is controversial, serologic tests were obtained only in less than half of the cases (21/48) of DFP reported in the literature. Even positive history of recurrent labial HSV lesions or previous VZV infection, which is considered valuable anamnestic indicator, were often underestimated or not even investigated.

Alternatively, the incidence of DFP after stapedectomy ranges between 0.07% and 1.4% in the literature, corresponding to 1/450 [1] to 1/1000 of operated ears. [4] A higher incidence has been reported in more limited series, (1.4%–37.5%), particularly those employing lasers. [4, 6, 11, 33]

Considering the possible reduction of natural immunity following the mass VZV vaccination campaign, one might expect a recrudescence of VZV after stapedectomy; instead, a relevant increase in the incidence of DFP has not yet been observed.

When evident, typical conchal blebs of RH syndrome appear later than the facial paresis; electrophysiological tests do not differentiate post-surgical DFP from other types of facial paresis; and imaging after uncomplicated stapedectomies with DFP is not conclusive, although useful for possible medicolegal purposes to exclude iatrogenic lesions. Thus, presence of specific anti-VZV IgG and IgM should be checked for confirmation of etiology; special attention must be paid to prodromal symptoms, such as unexplained late pain (acute neuropathic otalgia). [28]

In conclusion, "Zoster sine herpete" is the most frequent pattern reported in literature and reactivation of VZV might be underestimated in clinical practice because of the lack of typical RH in DFP after stapedectomy.

Given the paucity of DFP, the universal preventive use of antivirals in stapes surgery is not warranted, except for selected cases. For this reason, the initial intense pain might indicate those cases who would benefit from immediate administration of antivirals.

Ethics Committee Approval: Ethics committee approval was received for this study from the internal ethical committee.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – D.Z.; Design - D.Z.; Supervision - F.D.B., D.Z.; Resources - D.Z..,; Materials - D.Z.; Data Collection and/or Processing - D.Z.; Analysis and/or Interpretation - F.D.B.; Literature Search - F.D.B.; Writing Manuscript – F.D.B., D.Z.; Critical Review - F.D.B., D.Z.

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