ORIGINAL ARTICLE

Sudden Sensorineural Hearing Loss after Pituitary Adenoma Resection—A Case Series with Literature Review

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Key words: transsphenoidal surgery for pituitary adenoma; obstructive hydrocephalus; ischemia of internal auditory arteries; sudden sensorineural hearing loss; tinnitus

Objective Complications after transsphenoidal surgery for pituitary adenoma have been well documented in the literatures, but the occurrence of delayed sudden sensorineural hearing loss (SNHL) after pituitary adenoma resection is extremely rare. In this study three cases who developed sudden SNHL 3 to 7 days after pituitary adenoma surgery without experiencing cerebrospinal fluid leak or meningitis were presented, and the possible causes of SNHL were discussed.

Methods Three cases with sudden hearing loss after transsphenoidal surgery for pituitary adenoma were reviewed. The past medical history, onset of sudden hearing loss, accompanying symptoms such as headache, tinnitus, dizziness and aural fullness, and the post-operative MRI images, therapy, and hearing results were reported.

Results Three cases developed profound sudden SNHL on the 3rd to 7th post-operative day, all accompanied by prior headache, tinnitus and dizziness. One patient developed episodic vertigo, ear fullness accompanying with fluctuating hearing loss in the first post-operative month. Two patients had past medical history of arteriosclerosis and coronary heart disease or cerebral infarction. Two of three demonstrated obstructive hydrocephalus on MRI on the first post-operative day. Under treatment with prednisone orally, dexamethasone intratympanic injection, neurotrophic and vasodilatation drugs for 3 to 8 months, hearing of all three improved partially. Obstructive hydrocephalus and ischemia might be responsible for the hearing loss.

Conclusion Post-operative obstructive hydrocephalus and ischemia of labyrinthine arteries might lead to the delayed SNHL after transsphenoidal surgery for pituitary adenoma.

S UDDEN sensorineural hearing loss (SNHL) after non-otologic surgery is exceedingly rare.^[1] To our knowledge sudden SNHL after transsphenoidal surgery (TSS) for pituitary

adenomas has never been reported in the English literatures. A series of three cases of sudden SNHL after pituitary adenomas surgery were reported and the possible causes and management for SNHL were discussed.

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PATIENTS AND METHODS

Patient selection

Three cases diagnosed with sudden hearing loss after

transsphenoidal surgery for pituitary adenoma were included and reviewed in the present study. All of them were from the Department of Otolaryngology of Peking Union Medical College Hospital from 2017 to 2019. Age, gender, the past medical history, the onset of sudden hearing loss, accompanying symptoms such as headache, tinnitus, dizziness and aural fullness, and the post-operative MRI images, therapy, and hearing were recorded in detail.

Written informed consent was obtained from the patients. This study was granted an exemption from the Institutional Review Board of our hospital, China.

Auditory assessment

All patients underwent otoscopic examination, pure tone air and bone conduction audiometry (AC40 Diagnostic Audiometer; Interacoustics, Middelfart, Denmark) at 250, 500, 1000, 2000, 4000, and 8000 Hz at the first visit and various follow-ups. Tympanometry was used to measure the middle ear pressure (AZ26 Impedance Audiometer; Interacoustics, Denmark). Auditory brainstem response (ABR) were assessed.

RESULTS

Demographic, symptoms, and post medical history of the three patients of sudden SNHL after transsphenoidal surgery for pituitary adenomas are recorded in **Table 1**. None of the patients had a family history of hearing loss; a history of noise exposure; a history of ear surgery, a history of hearing loss, vertigo, tinnitus; a history of otitis media, or any other consistent otological complaints; or a history of ototoxic drug use and autoimmune disease. Both pure tone audiogram (PTA) and ABR all revealed bilateral profound SNHL (air-bone gap <7.5 dB in PTA, >95 dB in ABR) at the first visit. Air conduction thresholds in pure tone audiometry of the three patients before and after steroid and vasodilator therapy are recorded in **Table 2**. The details were demonstrated below.

Case 1 A 33-year-old woman underwent a microscopic TSS for non-functioning pituitary adenomas. The 1-hour operation was uneventful without evidence of large quantity bleeding, cerebrospinal fluid (CSF) leak, and no ototoxic drugs were used intra- or post-operatively. Nitrous oxide and controlled hypotension

Table 1. Demographic, symptoms, and post medical history of the three patients of sudden SNHL after transsphenoidal surgery for pituitary adenomas

Case	Age (yrs)	Gender	Onset (d)	Symptoms					Post medical history					
				Tinnitus	Ear-fullness	SSNHL	Vertigo	Headache	HTN	DM	HL	CAD	CVD	AID
1	33	Female	7	+	+	+	+	+	No	No	No	No	No	No
2	68	Female	3	+	+	+	+	+	Yes	No	No	No	Yes	No
3	63	Male	3	+	+	+	+	+	Yes	No	Yes	Yes	No	No

SNHL: sensorineural hearing loss; onset (d): onset days of sudden SNHL after transsphenoidal surgery for pituitary adenomas; SSNHL: sudden SSNHL; HTN: hypertension; DM: diabetes mellitus; HL: hyperlipidemia; CAD: coronary artery disease; CVD: cerebrovascular disease; AID: autoimmune disease history or lab suggesting autoimmune disease.

Table 2. Air conduction thresholds in pure tone audiometry of the three patients before and after steroid and vasodilator therapy (kHz)

Case	Time	Left						Right					
		0.25	0.5	1	2	4	8	0.25	0.5	1	2	4	8
1	Baseline	85	85	105	105	100	NR	65	80	85	105	120	NR
	1 month	30	45	40	45	60	75	10	10	10	45	85	90
	3 months	30	40	30	20	60	75	10	10	10	35	80	95
2	Baseline	NR	NR	NR	NR	NR	NR	NR	110	100	120	110	NR
	1 month	85	95	90	85	80	95	65	85	85	90	85	90
	3 months	50	70	80	70	70	90	30	60	80	75	75	90
	8 months	15	50	70	75	65	80	15	50	70	75	80	90
3	Baseline	80	90	100	95	NR	NR	85	90	90	85	95	90
	6 months	50	45	50	85	90	100	40	45	40	25	15	30

NR: no response.

were not applied, blood pressure (BP), pulse rate and perfusion pressures were well-maintained during general anesthesia. She was otherwise healthy without any special medical history (**Table 1**). On the seven days after pituitary surgery she developed ear-fullness, vertigo, and bilateral sudden deafness without neck stiffness, fever or confusion. No other cranial nerve deficits were present and her blood pressure was in normal range. CSF pressure, routine examination and biochemical test were normal. Bacteria culture of CSF was negative. Routine blood tests were normal. Systemic autoimmune disease was ruled out by rheumatologic workup. MRI demonstrated postoperative changes of pituitary area without hematoma, hemorrhage or stroke. CT scanning of the temporal bones was normal without enlarged vestibular aqueduct. Otoscopy was normal. PTA and ABR revealed bilateral profound SNHL (air-bone gap <7.5 dB in PTA, >95 dB in ABR) on post-operative day 7. She was referred to Otorhinolaryngology clinic and immediately received vasodilators, neurotrophic drug and steroids. Ginkgo biloba extract 40 mg tid was taken orally for one month, and prednisone 60 mg qd was given for one week then reduced by 10 mg every week for another 3 weeks. Intratympanic injection of dexamethasone 5 mg per week lasted for total 12 weeks. Her hearing improved gradually every week, and stabilized at the end of 12-week treatment (**Table 2**). Her hearing recovered to almost normal, leaving only residual high-frequency SNHL bilaterally. The hearing remained well after 2-year follow-up.

Case 2 A 68-year-old woman was diagnosed with non-functioning pituitary adenomas by MRI and endocrine hormone assessment. She had hypertension for 18 years with BP_{max} 170/90 mm Hg. Her BP could be controlled at 140-150/80-90 mm Hg with amlodipine besylate 2.5 mg qd and captopril 50 mg qn. Old cerebral infarction was discovered accidentally 3 years ago without symptoms. One month ago, she felt numbness of nasolabial groove and her speech was not fluent. She was diagnosed with acute cerebral infarction in the left paraventricular area, and the symptoms disappeared after alprostadil injection for one week. Transsphenoidal partial resection for pituitary adenomas was successful, and no fever or evidence of CSF leak was found intra- or post-operatively. On post-operative day 3 she complained of dizziness, vomiting, loud tinnitus in both ears, loud noise in the brain and sudden hearing loss bilaterally (**Table 1**). She had

no stiff neck or other cranial nerve dysfunctions. CSF examination after hearing loss revealed no meningitis and CSF pressure on lumbar puncture was in normal range. She was referred to Otorhinolaryngology clinic on post-operative day 8. PTA and ABR demonstrated bilateral profound SNHL. Oral prednisone 1 mg/kg was prescribed per day for 1 week then tapered 10 mg every week, intratympanic injection of dexamethasone 5 mg/ml was administered once a week for 4 months, and vasodilator alprostadil 10 µg was intravenously injected qd for 2 months. Neurotrophic drug gintonin 40 mg tid was taken orally for 8 months. MRI on the first post-operative day revealed dilatation of bilateral ventricles and third ventricle. MRI 1 month after the surgery showed reduction of hydrocephalus of bilateral ventricles and third ventricle. Her bilateral hearing partially recovered (**Table 2**).

Case 3 A 63-year-old man with a non-functioning pituitary adenomas revealed by MRI (**Fig. 1A, 1B, 1C**) and normal endocrine function sought treatment who had a history of 7 years of visual disturbance and 4 years of headache. He had hypertension for 30 plus years, hyperlipemia for 20 years, and underwent coronary stent implantation 5 years ago. Transsphenoidal partial resection of pituitary adenomas was performed without CSF leakage intra- or post-operatively. The patient was under hydrocortisone 5 mg tid administration for 1 month followed by gradual drug reduction.

On post-operative day 1 he had bad headache, severe bilateral tinnitus and good hearing, and on post-operative day 3 he had difficulty in communicating with his family because of rapid hearing loss accompanying with vertigo for 1 hour. Then he experienced episodic rotational vertigo lasting for 2 to 4 hours accompanying with tinnitus, aural fullness and fluctuating hearing loss in the first post-operative month (**Table 1**). He had never had these problems before the surgery. After the operation his temperature was in normal range without stiff neck and he had no other cranial nerve dysfunction. He was referred to Otorhinolaryngology clinic on post-operative 1 month with a chief complaint of profound SNHL on audiometry in both ears. He orally took gintonin 40 mg tid for 5 months. Audiometry at 6 months post-operatively demonstrated mild SNHL in left ear and severe SNHL in right ear (**Table 2**). The headache and vertigo disappeared while bilateral tinnitus still bothered him.

His preoperative MRI showed a large snowman shaped mass inside and above the sellar region and the

right lateral ventricle was a little enlarged compared with the left. MRI of postoperative day 4 showed the mass in the sellar region enlarged, with both high and low signal intensity in it which indicated bleeding, and compressed the right hypothalamus and third ventricle. The bilateral ventricles were enlarged, with the right side enlarged more obviously, indicating hydrocephalus (**Fig. 1D, 1E, 1F**). MRI of 3 months postoperatively showed the residual mass in the sellar region was significantly diminished, with the bleeding significantly absorbed. The enlarged left and right lateral ventricles were reduced but not to the normal size, indicating that hydrocephalus did not relieve completely (**Fig. 1G, 1H, 1I**).

DISCUSSION

Sudden SNHL after non-otologic surgery, first

reported by Jaffe in 1967, is a rare complication and sporadically reported in various procedures including ophthalmologic, dental, orthopedic, abdominal, cardiovascular and neurosurgical. Cardiopulmonary bypass surgery and surgeries associated with loss of CSF are two main categories of surgery mostly leading to sudden SNHL.^[1] Although general complications after transsphenoidal surgery for pituitary adenomas have been well documented,^[2] and conductive hearing loss caused by nasal packing after pituitary operation is common, as far as we know sudden SNHL has never been reported in the literatures. Here we reported three cases of delayed profound sudden SNHL after pituitary operation and discussed the possible mechanisms.

Hearing loss induced by CSF loss was well documented. Compensatory endolymphatic hydrops caused

Figure 1. MRI results of case 3. Preoperative coronal T1 weighted (A), T2 weighted (B) and T1 weighted contrast-enhanced images (C) showing a large snowman shaped mass inside and above the sellar region (arrows). The right lateral ventricle is a little enlarged compared with the left.

Four days after the surgery, coronal T1 weighted (D), T2 weighted (E) and T1 weighted contrast-enhanced images (F) showing that the mass in the sellar region is increased in size, with both high and low signal intensity indicating bleeding inside the mass (arrowheads). Both the left and right lateral ventricles are enlarged, with the right side enlarged more obviously, indicating hydrocephalus. About three months after the partial tumor resection surgery, coronal T1 weighted (G), T2 weighted (H) and T1 weighted contrast-enhanced images (I) showing that the residual mass in the sellar region is significantly diminished, with bleeding significantly absorbed. However, both the left and right lateral ventricles still do not return to their normal size.

by CSF loss is the most popular theory of hearing loss. There is a direct communication between CSF and perilymph through the cochlear aqueduct. The pressures of CSF, perilymph and endolymph are equal in normal conditions. Loss of CSF leads to decreased CSF pressure and perilymph hypotension, resulting in a compensatory expansion of endolymph. Compensatory hydrops of endolymph leads to hearing decrease and vertigo, mimicking the symptoms of menière's disease.^[3] Hearing loss induced by CSF loss usually showed bilateral or unilateral, and flat or low frequency predominant. Most hearing loss could recover within 3 months,^[4, 5] although a few sporadic cases left permanent hearing loss.^[3] However, no evidence of CSF leak was found intra- or post-operatively in all the 3 patients, so CSF leakage was not the plausible cause of these 3 cases.

Meningitis could spread infection from the subarachnoid space to inner ear through the cochlear aqueduct, therefore, resulting in labyrinthitis. Labyrinthitis usually demonstrates bilateral profound whole frequency hearing impairment. The meningitis patients usually show distinct symptoms or signs. Though all the patients had bilateral profound whole frequency hearing impairment, none of them experienced CSF leakage or any typical symptoms or signs clinically consistent with meningitis. The CSF and blood analysis of case 1 and 2 immediately after hearing impairment failed to demonstrate evidence for bacterial infection. So meningitis was not a possible cause of postoperative sudden SNHL in these cases.

Ototoxicity is another possible cause of SNHL. The patients did not use ototoxic drugs either topically or systemically intra- or post-operation, so ototoxicity can be excluded from the causes of hearing loss in the current cases.

Nitrous oxide during general anesthesia may cause SNHL by increasing middle ear pressure and perilympatic fistulas.^[6] Large vestibular aqueduct may also result in SNHL and vertigo while cranial pressure changes.^[7] Nitrous oxide and large vestibular aqueduct can be excluded from the causes of SNHL in these cases, since nitrous oxide was not used in anesthesia and large vestibular aqueduct was not found on their CT scanning of temporal bones.

Ischemia of internal auditory arteries induced by vasospasm would cause sudden SNHL.^[8] Cerebral vasospasm causing delayed cerebral ischemia and neuropathy after TSS has been reported.^[9] Because the hair cells are supplied almost exclusively by lab-

yrinthine artery, they are high oxygen consumption and poor tolerance to ischemia. Son *et al.*^[10] reported a similar case: a young woman developed profound bilateral SNHL accompanying with bilateral ear fullness and tinnitus, without vertigo and other neurologic deficits following cardiopulmonary bypass immediately. Her hearing recovered almost completely one week after surgery without any treatment. Case 2 and 3 of our report cohort had cardiovascular and cerebrovascular diseases previously, they were at high risk to the attack of cerebral vasospasm in brain surgery and had poor tolerance to ischemia. Their hearing recovered gradually after steroids, vasodilators and neurotrophic drug administration every week, supporting vascular involvement might be one of the possible causes of SNHL. So ischemia of internal auditory arteries might be a contributing factor to sudden SNHL of the three cases, although there was no visible stroke exhibited by post-operative radiological scanning, this fact suggested that ischemia occurred in a limited area and internal auditory artery might be more susceptible to ischemic insults.

Autoimmune SNHL was difficult to diagnose since the immune workup for primary autoimmune inner ear disease could be negative. A favorable response to the steroid could be considered a clinical diagnostic criterion for autoimmune SNHL.^[11] Case 1 developed simultaneously bilateral sudden SNHL with vertigo 7 days after pituitary adenomas surgery, and had favorable response to steroid which suggested the possibility of autoimmune inner-ear disease. Secondary autoimmune SNHL induced by systemic autoimmune diseases was ruled out by normality of rheumatologic workup, however it remains to be discussed whether primary autoimmune inner ear diseases can lead to SSNHL.

Hydrocephalus or fluctuation of intracranial pressure after cranial surgery might be one of the causes of SNHL. The correlation between SNHL and hydrocephalus has been reported.^[12] The mechanism of hearing loss caused by hydrocephalus remains unclear. Some authors proposed "the hydrodynamic theory"^[13] which stated that abnormally high or low CSF pressure is transmitted to the inner ear fluids (perilymph and/or endolymph) *via* the cochlear aqueduct and/or endolymphatic sac. A minimal pressure difference amongst endolymph and perilymph can determine displacement of the Reissner's membrane and could cause auditory-vestibular impairment, manifesting as SNHL, vertigo, tinnitus, aural fullness. Post-operative mild obstructive

hydrocephalus was demonstrated in case 2 and 3 on MRI performed on first or fourth post-operative day. Since hemorrhage of the tumor bed induced swollen of the pituitary, which in turn compressed and influenced CSF circulation, and obstructive hydrocephalus developed afterwards. On post-operation day three, both patients developed bilateral sudden SNHL. Patient 3 also experienced episodic rotational vertigo accompanying with tinnitus, aural fullness and fluctuating hearing loss in the first post-operative month, mimicking the symptoms of menière's disease. After treatment of steroid, vasodilator and neurotrophic drugs, MRI revealed hydrocephalus lessened on post-operative 1 month or 3 months, their hearing also gradually recovered and headache and dizziness also diminished. Hydrocephalus could have a similar effect on both ears as in our patients, so we propose that hydrocephalus might be one of the causes of hearing loss in case 2 and case 3.

Topical epinephrine used on round window membrane reduced cochlear blood flow during middle ear surgery was reported, and cochlear blood flow recovered to baseline slowly (>10 min) after epinephrine removal. We thought that prolonged decrease in cochlear blood flow with round window membrane application of epinephrine may compromise sensory function and could account for the occasional unexplained SNHL or tinnitus associated with middle ear procedures that use topical epinephrine.^[14] Topical application of a cotton soaked in epinephrine is effective to lessen bleeding in TSS surgery. Epinephrine spreading to middle ear through long and narrow eustachian tube was extremely rare, since the cotton is usually half dry and only placed on anterior and middle nasal septum incision site once or twice. The possibility of epinephrine diffusing into middle ear during TSS surgery is much less than that during functional endoscopic sinus surgery for nasal polyps or tumors. Up to now SNHL after functional endoscopic sinus surgery has not been reported, so topical epinephrine used on anterior nasal septum induced SNHL should be excluded in these cases.

This study reminds surgeons that, when headaches, tinnitus, dizziness and aural fullness aggravate after pituitary adenomas resection, sudden SNHL should be thought of although it occurs rarely. Delayed diagnosis and treatment can interfere with patient's hearing and verbal communication.

In conclusion, ischemia of labyrinthine arteries induced by cerebral vasospasm in high risk people with

a history of cardiovascular and cerebrovascular diseases and obstructive hydrocephalus or fluctuation of intracranial pressure caused minimal pressure difference amongst endolymph and perilymph which makes displacement of the Reissner's membrane, may be the two main reasons of SNHL after TSS for pituitary adenomas. Although the usage of steroid relieved symptoms of case 1, whether her SNHL is induced by autoimmune disease is uncertain. Steroid and vasodilators administrated early would benefit hearing recovery.

Conflicts of Interest Statement

The authors declare no conflicts of interest.

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论著

垂体瘤切除术后突发感音神经性聋—病例系列报告及文献复习

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摘要

目的 经蝶垂体瘤术后患者较少出现延迟的突发性感音神经性聋。本研究报告了3例垂体瘤患者, 术后无脑脊液漏或脑膜炎, 但是在术后3至7日发生突发性感音神经性聋, 并讨论了可能的致聋原因。

方法 对3例经蝶垂体瘤术后延迟出现突发性感音神经性聋病例, 报告其病史、突发性聋的发生时间、伴随症状如头痛、耳鸣、眩晕、耳闷等, 以及术后MRI表现、治疗、听力恢复等情况。

结果 术后3至7日突发极重度感音神经性聋的3例患者, 听力下降前全都伴发头痛、耳鸣、眩晕。1例有间断反复发作的眩晕、耳闷、波动性听力下降, 持续至术后1个月。2例有动脉硬化、冠心病史或脑梗死史。3例患者中2例术后第1天MRI显示梗阻性脑积水。在口服泼尼松、鼓室注射低塞米松、服用神经营养药物和扩血管药物3至8个月之后, 3例患者听力均有部分恢复。术后梗阻性脑积水和内听动脉缺血可能造成术后耳聋。

结论 经蝶垂体瘤术后梗阻性脑积水和迷路动脉缺血可能引起延迟出现的突发性感音神经性聋。

关键词: 经蝶垂体瘤切除术; 阻塞性脑积水; 内听动脉缺血; 突发性感音神经性聋; 耳鸣

中文摘要

基于生物信息学分析肾透明细胞癌预后相关关键基因

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摘要

目的 识别与肾透明细胞癌预后相关的关键基因。

方法 基于生物信息学分析技术对GEO数据库中的62个肾透明细胞癌样本和54个正常肾组织的数据集(GSE12606, GSE36895和GSE66272)进行分析。首先在GEO2R和J Venn网站上获取差异表达基因, 之后采用GO和KEGG对基因进行功能注释; 在使用STRING网站构建PPI网络后, 采用Cytoscape软件的MCODE App对核心基因进行筛选; 最后利用GEPIA网站分析与生存率有关的核心基因。

结果 我们共发现648个差异表达基因, 包括222个上调表达基因和426个下调表达基因。PPI蛋白网络分析共发现28个表达上调的核心基因, 其中7个核心基因(*CCNE2*, *CDK1*, *CDC6*, *CCNB2*, *BUB1*, *TTK*和*PTTG1*)富集于细胞周期, 4个(*CCNE2*, *CDK1*, *CCNB2*和*RRM2*)富集于p53信号通路。GEPIA生存率分析发现:*CDK1*, *CCNB2*, *RRM2*, *BUB1*, *PTTG1*与肾透明细胞癌患者的生存率密切相关。肾透明细胞癌患者*BUB1*, *CCNB2*, *PTTG1*和*RRM2*等4个关键基因的表达量高于正常人群($P<0.05$)。

结论 *BUB1*、*CCNB2*、*PTTG1*、*RRM2*等4个上调差异表达基因可能是肾透明细胞癌患者预后关键预测基因。

关键词: 肾透明细胞癌; 生物信息学分析; 差异表达基因