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Original Article

Clinical Analysis of 3D–Fluid Attenuated Inversion Recovery and T1volume interpolated body examination Sequences on Delayed Gadolinium–Enhanced Scanning in Ramsay Hunt Syndrome

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BACKGROUND: Through the clinical analysis of 4 clinically confirmed cases of delayed gadolinium enhancement of Ramsay Hunt syndrome 3D-Fluid Attenated Inversion Recovery'and 'T1volume interpolated body examination (3D-FLAIR and T1VIBE) sequences, the more suitable sequences and pathologically damaged tissue sites of deep tissues of Ramsay Hunt syndrome by magnetic resonance imaging gadolinium enhancement were preliminarily explored.

METHODS: From October 2020 to March 2021, 4 clinically confirmed patients with Ramsay Hunt syndrome, 2 males and 2 females, aged 27-63, were continuously collected in the hospital otology clinic. Siemens Avento 1.5T magnetic resonance imaging 3D-FLAIR and T1VIBE sequence-delayed gadolinium enhancement scans and serological laboratory tests were performed, respectively, and corresponding antiviral and anti-inflammatory therapy was given.

RESULTS: The magnetic resonance imaging gadolinium enhancement of 4 cases of Ramsay Hunt syndrome was as follows: 3D-FLAIR sequence delay of 4.5 hours scanning 4 patients labyrinthine and/or middle ear signal was enhanced at the same time as the healthy side; T1VIBE sequence scanning disease in 3 cases of vestibular nerve development was enhanced than the healthy side, 2 cases of facial nerve development was enhanced than the healthy side, and 2 cases of cochlear nerve development was enhanced than the healthy side. All 4 patients were cured with related treatment.

CONCLUSION: Through the comparison of 3D-FAIR and T1VIBE sequence of 4.5 hours delay before intravenous gadolinium injection and 4.5 hours delay after intravenous gadolinium injection in 4 patients with Ramsay Hunt syndrome, it was found that (i) 3D-FLAIR sequence delay of 4.5 hours scan was more likely to show whether the inner ear labyrinth barrier permeability increased and (ii) Ramsay Hunt syndrome deep ear tissue damage can be manifested as labyrinthitis, vestibular cochlear neuritis, facial neuritis, and otitis media.

KEYWORDS: Varicella-zoster virus labyrinthitis gadolinium enhancement 3D-FLAIR T1vibe

INTRODUCTION

The ear disease caused by the varicella-zoster virus, known as ear zoster, also known as Ramsay Hunt syndrome, was first described by Professor Ramsay Hunt in the United States in 1907.[1] It typically presents with severe ear pain, otozoster zoster, and ipsilateral peripheral facial paralysis.[2] Scholars at home and abroad have studied this disease many times through ordinary Magnetic resonance imaging T1 weighted imaging, T2 weighted imaging, and volume interpolated body examination and 3D-Fluid Attenuated Inversion Recovery sequence non-enhanced or non-delayed enhancement scanning, but most of them describe Ramsay Hunt syndrome in the facial nerve, vestibular nerve, cochlear nerve, and inner ear after the acute phase of the development enhancement,[3-8] so far there is no description of MRI 3D-FLAIR and T1VIBE sequence delayed gadolinium enhancement scan for the acute phase of the disease. From October 2020 to March 2021, the author successively received 4 patients with Ramsay Hunt syndrome

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in the hospital otology clinic and underwent 3D-FLAIR and T1VIBE sequence gadolinium-enhanced delayed scanning and serological laboratory examinations, respectively, and found that the inner ear of the 4 patients was significantly affected higher than the healthy side and was cured by active antiviral and anti-inflammatory treatment. It is reported later.

MATERIAL AND METHODS

Research Objects

After reviewing the literature, Ramsay Hunt syndrome, also known as auricular shingles, is caused by the varicella-zoster virus, and its symptoms and signs are severe ear pain, ear herpes, and III-XII cranial nerve invasion and dysfunction. Based on this, the hospital ear clinic collected 4 cases of Ramsay Hunt syndrome consecutively from October 2020 to March 2021, including 2 males and 2 females, aged 27-63 years old, with an average age of 45.75 years. The common clinical symptoms and signs of 4 patients were ear pain, herpes zoster in the pinna and external auditory canal, vertigo, and hearing loss, among which case 2 and case 4 had peripheral facial paralysis of varying degrees, and the specialist examination and laboratory tests were shown in Table 1. This study was conducted after review and approval by the The People's Hospital of Dongsheng District, Ordos City Ethics Committee (2020-s001). Before starting the study, consent was obtained from each patient and an informed consent form was signed.

Inspection Methods

Inner ear gadolinium-enhanced examination was performed in all 4 patients by intravenous injection of gadolinium-enhanced SIEMENSE Avanto 1.5T MRI-related sequence. The contrast agent is gadopentetate meglumine injection (produced by Beijing Beilu Pharmaceutical Co., Ltd., China, the specification is 20 mL: 9.38 g), the dosage is 0.4 mL/kg × body weight, and the method is through the cubital vein at a rate of 3.0 mL/min injected into the body. The specific sequence and parameters of the scan are as follows: (i) The fast spin echo sequence (3D-SPACE) using axial 3-dimensional multi-reversal angle optimization and contrast sampling is TR 1200 ms, TE 265 ms, and the spatial resolution is 0.5 mm × 0.5 mm × 1 mm, scan time 320 seconds; (ii) fluid-suppressed inversion recovery sequence (3D-SPACE-FLAIR) using 3-dimensional multi-inversion angle optimized contrast sampling (3D-SPACE-FLAIR) field of view (FOV) 220 mm × 174 mm, TR 6000 ms, TE 355 ms, Time of inversion (TI) 2200 ms, matrix 248, slice thickness 1 mm, scan time 308 seconds.[9-11] (iii) T1VIBE sequence FOV 200 mm, TR 9.0 ms, TE 2.4 ms, matrix 192, slice thickness 1 mm, scan time 278 seconds [12,13]

MAIN POINTS

- The purpose of this study is to explore the lesion status of deep ear tissue in Ramsay Hunt syndrome by magnetic resonance imaging 3D-FLAIR and T1VIBE sequence delayed scanning for 4.5 hours.
- The 3D-FLAIR sequence scanning with a delay of 4.5 hours is easier to show whether the permeability of the blood labyrinth barrier in the inner ear is increased.
- Ramsay Hunt syndrome deep ear tissue damage can be manifested as labyrinthitis, vestibulocochlear neuritis, facial neuritis, and otitis media.

Table 1. Clinical Data of 4 Patients with Varicella-Zoster Labyrinthitis

Serial No.	Sex	Age (Years)	Site	Course (Days)	Hearing (Average dBHL)		Spontaneous Nystagmus		Dual Temperature test		Main Symptoms and Signs		Blood tests Positive Result
					PR-T	PO-T	PR-T	PO-T	PR-T	PO-T	PR-T	PO-T	
1	Female	63	Left	6	42.85	30.71	Horizontal right	—	Left weak Right normal	Double normal	Earache, deafness, vertigo, herpes of the external ear	—	Positive for varicella zoster virus IgM
2	Male	63	Right	4	39.85	20.71	Horizontal left	—	Right weak Left normal	Double normal	Earache, deafness, vertigo, herpes of the external ear, facial nerve H–B III grade	—	Positive for varicella zoster virus IgM, high white cells of blood routine, fast ESR
3	Male	30	Left	6	12.14	7.85	Horizontal right	—	Left weak Right normal	Double normal	Earache, ear tightness, dizziness, herpes of the external ear	—	Positive for varicella zoster virus IgM
4	Female	27	Right	3	29.28	5.00	Horizontal left	—	Right weak Left normal	Double normal	Vertigo, nausea, vomiting, deafness, herpes of the external ear, facial nerve H–B II grade	—	Critical for varicella-zoster virus IgM

—, disappearance of symptoms or signs; H–B, House–Brackmann; PO-T, post-treatment; PR-T, pre-treatment; Serial No, serial number.

Gadolinium-enhanced qualitative and quantitative determinations in the current MRI sequence, only the ADC value measured by ADC map, T1 value and T2 value measured by T1maping and T2maping are relatively stable. As for the T1VIBE and 3D-FLAIR sequences selected in this study, since all patients were scanned under the same sequence conditions with the same equipment, the measured MRI values were also relatively stable and available. Therefore, the specific method of the author in the qualitative determination is that 2 MRI physicians with the title of deputy chief physician or above mainly observe the facial nerve, vestibular nerve, and cochlear nerve of the affected side and the healthy side of the same image in the same sequence of T1VIBE and 3D-FlAIR for 4.5 hours. The visual signal level of the inner ear is used as a qualitative basis. If the macroscopic signal of the affected side is higher than that of the unaffected side, the point or segment with stronger visualization of the corresponding structures of the bilateral facial nerve, vestibular nerve, cochlear nerve, and inner ear is used as the point or segment for intensity calculation. Then, the MR value of the corresponding point or segment is measured by the MRI post-processing workstation tool. The area of interest of the points or segments measured on both the affected side and the unaffected side is 0.01 square centimeters. Referring to the facial nerve enhancement measurement calculation method by Li Ying et al[14] and combining the characteristics of the vestibular nerve, cochlear nerve, and inner ear, the calculation method of this study is formulated as follows: facial nerve, vestibular nerve,cochlear nerve in the T1VIBE images of the affected side and the healthy side, each position of the inner ear on the 3D-FLAIR image is at least the average value of its 3 axial levels; if the difference between the calculated value on the affected side and the calculated value on the healthy side is less than 40, it is judged that there is no difference in the development of the affected side and the healthy side. If the difference between the calculated values of the affected side and the healthy side is greater than 40, the development is enhanced.

Examination pure tone audiometry, spontaneous nystagmus, temperature test, and laboratory examination.

Treatment: (i) Intravenous infusion of acyclovir powder for 7 days-14 days, dose 10 mg/kg, q8h; (ii) Intravenous infusion of methylprednisolone for 5 days, dose 2.5 mg/kg, qd; and (iii) intramuscular injection of mouse nerve growth factor for 7 Day, dose 30ug/time, qd.

RESULT

Gadolinium-enhanced showed as follow: Case 1, the left inner ear, middle ear and vestibular nerve were significantly enhanced compared to the contralateral side, see Figures 1-4, and the measured MRI values were shown in Table 2 and 3. Case 2 right inner ear, middle ear, facial nerve were significantly enhanced compared to the contralateral side, see Figures 1, 2, 5 and 6, and the measured MRI values were shown in Tables 2 and 3. Case 3, the left inner ear, vestibular nerve and cochlear nerve were significantly enhanced than the contralateral side, as shown in Figures 3, 4, 7 and 8, and the measured MRI values are shown in Tables 2 and 3. Case 4, the right inner ear and facial nerve, vestibular nerve, cochlear nerve were significantly higher than those of the opposite side, as shown in Figures 3-10. The measured MR values are shown in Tables 2 and 3.

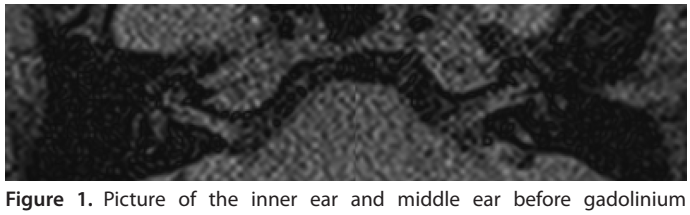

Figure 1. Picture of the inner ear and middle ear before gadolinium enhancement in case 2 3D-FlAIR sequence.

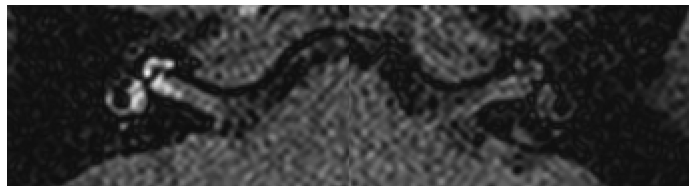

Figure 2. Case 2: picture of 3D-LFLAIR sequence gadolinium-enhanced scan of a labyrinthine middle ear with a delay of 4.5 hours.

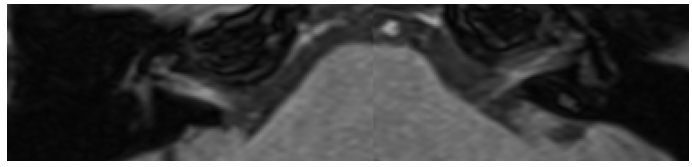

Figure 3. Picture of facial nerve before gadolinium enhancement in case 2 T1VIBE sequence.

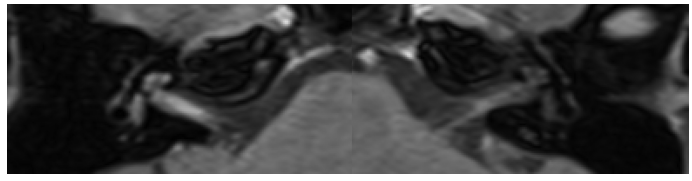

Figure 4. Picture of TVIBE sequence gadolinium-enhanced scan with a delay of 4.5 hours.

Prognosis

All 4 patients were cured. Case 1 after 10 days of treatment, the patient's headache and earache disappeared, and his hearing recovered. He only had symptoms of dizziness, and he was able to take care of himself completely. After another 2 months, the dizziness disappeared, and the vestibular function and facial nerve function was normal. The follow-up was normal for 1 year. Case 2 after 7 days of treatment, the vertigo disppeared, and the hearing recovered, and the facial paralysis was obviously relieved. Follow up a case by regular visits to 7 days again, the facial paralysis disappears, and the symmetrical movement of the muscles innervated by bilateral facial nerves is as usual. The 1-year follow-up was as usual. Case 3 after 7 days of treatment, the patient's vertigo symptoms disappeared, the herpes-like skin lesions on the left auricle were healed, and the hearing recovered, vestibular function, and facial nerve function of the patients were normal during the 1-year follow-up. Case 4 after 7 days of treatment, the hearing became normal, and vertigo disappeared After another 7 days of treatment, peripheral facial paralysis disappeared, the 1-year follow-up,all function was as usual.

In previous studies on Ramsay Hunt syndrome, most of the deep ear tissue changes observed by MRI T1WI and T2WI sequence gadolinium-enhanced scans were changes of the facial nerve, vestibular nerve, and cochlear nerve. So far, only MAKOTO SUGIURA and MI S. CHUNG et al reported in 2007 and 2015, respectively, that patients with Ramsay Hunt syndrome were scanned with non-enhanced

Table 2. Measurement of 3D-FLAIR Gadolinium-Enhanced Signal in 4 Patients with Varicella-Zoster Labyrinthitis

Serial Number	Part	Affected Side	Healthy Side	Two-Sided Difference	Ill-Side Result Judgment
1	Vestibular	232.0	157.0	75.0	++
	Cochlear base	275.0	166.0	109.0	++
	Cochlear midway	223.0	142.0	81.0	++
	Cochlear top turn	171.0	102.0	69.0	++
	Middle ear	116.0	58.0	58.0	++
	Vestibular nerve	602.0	436.0	166.0	++
2	Vestibular	270.0	133.0	137.0	++
	Cochlear base	207.0	108.0	99.0	++
	Cochlear midway	203.0	117.0	86.0	++
	Cochlear top turn	154.0	101.0	53.0	+
	Middle ear	154.0	55.0	99.0	++
3	Vestibular	172.0	110.0	62.0	++
	Cochlear base	152.0	110.0	42.0	+
	Cochlear midway	194.0	119.0	75.0	++
	Cochlear base	145.0	110.0	35.0	—
4	Vestibular	182.0	93.0	89.0	++
	Cochlear base	265.0	103.0	102.0	++
	Cochlear midway	268.0	127.0	141.0	++
	Cochlear top turn	192.0	130.0	62.0	++

1."+" indicates that the enhancement is 40 < the difference between the measured value of the affected side and the healthy side ≤ 60[13]; 2."++" indicates that the significant enhancement is 60 <the difference between the measured value of the affected side and healthy side; 3.The value of each position measured in the table is at least the average value of three levels or three measures points of one level level.

and non-delayed enhancement by 3D-FLAIR sequence and found that the inner ear signal of the affected side was higher than that of the healthy side.[6,8] However, the scanning time of the former was 9 days after the onset of the disease, which had exceeded 1 week, and the scanning time of the latter was not specified. The author also performed 3D-FLAIR sequence non-enhanced scans on 4 consecutive patients with Ramsay Hunt syndrome collected in this study but did not find that the inner ear signal on the affected side was higher than that on the healthy side in all 4 patients. But when they were intravenously injected with gadopentetate meglumine and scanned with a delay of 4.5 hours, it was found that the inner ear signal of all 4 patients was significantly higher than that of the healthy side. Why is this? Looking back on the medical history, it was found that the non-enhanced scan times of the 4 patients were 6d, 4d, 6d, and 3d after the onset, respectively, while the 3D-FLAIR non-enhanced scan time of the cases reported by MAKOTO SUGIURA was 9 days

Table 3. Measurement of T1VINE Gadolinium-Enhanced Signal in 4 patients with Varicella-Zoster Labyrinthitis

Serial Number	Part	Affected Side	Healthy Side	Two-Sided Difference	Ill-Side Result Judgment
1	Facial nerve	479.0	465.0	14.0	—
	Vestibular nerve	382.5	436.0	53.0	+
	Cochlear nerve	470.0	459.0	11.0	—
2	Facial nerve	489.0	401.00	88.0	++
	Vestibular nerve	431.0	394.0	37	—
	Cochlear nerve	445.0	436.0	9	—
3	Facial nerve	521.0	511.0	10	—
	Vestibular nerve	593.0	521.0	72.0	++
	Cochlear nerve	535.0	454.0	81.0	++
4	Facial nerve	182.0	93.0	89.0	++
	Vestibular nerve	544.0	344.0	200.0	++
	Cochlear nerve	390.00	267.00	123.00	++

1."+" indicates that the enhancement is 40 < the difference between the measured value of the affected side and the healthy side ≤ 60[13]; 2."++" indicates that the significant enhancement is 60 <the difference between the measured the measured value of the affected side and the healthy side; 3.The value of each position measured in the table is at least the average value of three levels or three measuring points of one level.

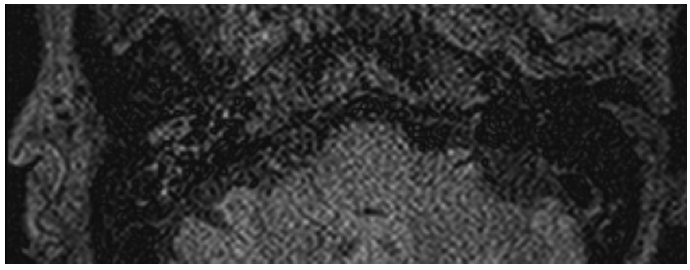

Figure 5. Picture of the inner ear before gadolinium enhancement in case 4 3D-FlAIR sequence.

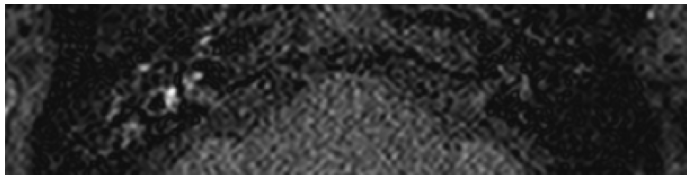

Figure 6. Case 4: picture of 3D-LFLAIR sequence gadolinium-enhanced scan of a labyrinthine with a delay of 4.5 hours.

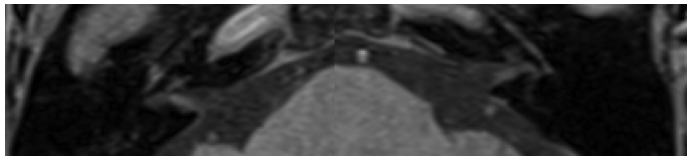

Figure 7. Picture of the facial nerve before gadolinium enhancement in case 4 T1VIBE sequence.

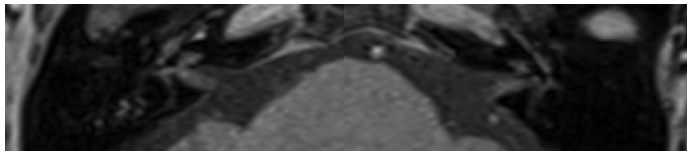

Figure 8. Picture of the facial nerve after gadolinium enhancement in case 4 T1VIBE sequence.

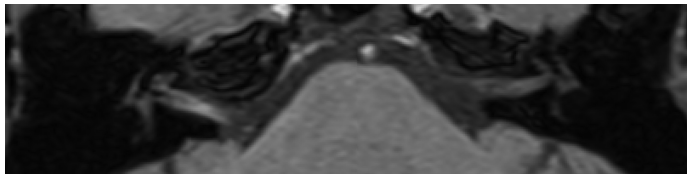

Figure 9. Picture of vestibulocochlear nerve before gadolinium enhancement in case 4 T1VIBE sequence.

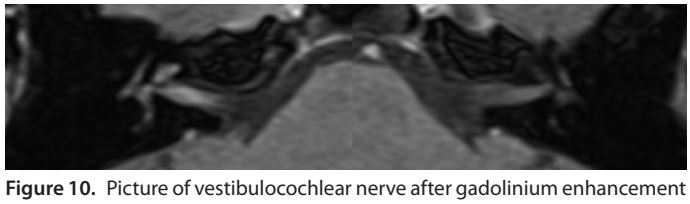

Figure 10. Picture of vestibulocochlear nerve after gadolinium enhancement in case 4 T1VIBE sequence.

after the onset, more than 1 week, which may suggest that if the 3D-FLAIR scan is performed within 1 week after the onset of Ramsay Hunt syndrome, it may not be easy to detect whether the signal in the inner ear is increased, and if the scan is delayed for 4.5 hours, it may be easier to detect whether the signal in the inner ear of the affected side is increased. As for why it is easier to detect the signal enhancement in the inner ear by delaying the scan for 4.5 hours, the author has explained it in another article "Gadolinium-Enhanced MRI Findings in Vestibular Neuritis." So why is it difficult to see that the signal on the affected side is higher than that on the healthy side in the early 3D-FLAIR non-enhanced scan? The reason may be that although the permeability of the blood labyrinth barrier of the inner ear increased in the early stage of Ramsay Hunt syndrome, it has not yet reached the level of exudation of serum proteins and other components. On the contrary, if the enhanced scan is performed, since the molecular weight of gadopentetate meglumine (938 Da) is significantly smaller than the molecular weight of serum protein (67 kDa), it is easier to pass through the blood labyrinth barrier, so it is easier to see that the signal on the affected side is higher than that on the healthy side. In addition, when the facial nerve, vestibular nerve, and cochlear nerve were scanned in this study, why the T1VIBE sequence was selected, and it was performed with a delay of 4.5 hours. The reason is explained in the article "Gadolinium-Enhanced MRI Findings in Vestibular Neuritis."

A review of the literature on Ramsay Hunt syndrome found that most authors focused on the varicella-zoster virus itself or its relationship to symptoms of III-XII cranial nerves, inner ear, and MRI damage,[15] without exploring the pathological significance of III-XII cranial nerve and inner ear damage. In all 4 patients, the inner ear was enhanced, the vestibular nerve was enhanced in 3 cases, the middle ear was enhanced in 2 cases, the facial nerve was enhanced in 2 cases, and the cochlear nerve was enhanced in 2 cases. Common pathological changes with contrast enhancement should include inflammation or hemorrhage, and the identification point of gadolinium-enhanced NMR 3D-FLAIR sequence and T1VIB sequence for acute and subacute inflammation and hemorrhage is 1. Inflammation did not increase or the enhancement was not obvious before the injection of gadolinium, but it was significantly enhanced after the injection of gadolinium; 2. Hemorrhage showed high signal before and after the injection of gadolinium. Obviously, the enhancement was obvious after gadolinium injection; (ii) the bleeding showed a high signal before and after the gadolinium injection. The 4 patients showed the former but not the latter, which indicates that the inflammatory reaction rather than bleeding should have occurred in the lesions of the 4 patients.[16] Combined with the results of laboratory tests such as routine blood tests, it means that the pathological mechanism of deafness and vertigo in these 4 patients may be mainly caused by aseptic inflammation of the labyrinth.[17] The vestibular nerve in case 1 and the vestibular nerve in case 3 and the cochlear nerve in case 4 shown by T1VIBE sequence, respectively, indicate that the onset mechanism of vertigo and deafness in these 3 patients is not only labyrinthitis but also vestibulo–cochlear nerve caused by varicella-zoster virus. Involvement of neuritis and enhanced facial nerve imaging in case 2 and case 4, respectively, resulted in facial nerve palsy. In addition, the mechanism of otitis media in case 2 may be caused by the reactivation of the varicella-zoster virus latent in the nucleus doubtful or glossopharyngeal ganglion.[14] In case 1, the enhanced signal in the middle ear was only displayed in the upper tympanic chamber and was relatively limited, so it did not cause conductive hearing loss. In case 2, the enhanced signal in the middle ear was displayed in the tympanic chamber, mastoid, and so on, and its signal enhancement range and MRI value were much higher than those of the healthy patient's ear, resulting in conductive hearing loss.

Although the all 3 patients had varicella-zoster signs of different degrees in the ear, laboratory serological examinations in case 1, case 2, and case 3 found that the varicella-zoster virus antibody Immunoglobulin M (IgM) was positive, and the varicella-zoster virus in case 4 was positive. The herpes zoster virus antibody IgM is borderline, which may be the test performed by the patient 3 days after the onset of the disease. The time is earlier, and the antibody IgM titer is in the process of becoming positive, so the result is borderline result. Because generally in the absence of acute varicella-zoster virus infection, the serological test of patients usually shows varicella-zoster virus antibody IgM negative. This further illustrates that the 4 patients were all in the acute phase of varicella-zoster infection.

When observing the clinical symptoms of the 4 cases of Ramsay Hunt syndrome, it was found that the main human dysfunctions were positional disturbance and hearing impairment. The former was manifested as non-rotating vertigo with immobility or immobility accompanied by nausea and vomiting and other symptoms. The latter has different degrees of hearing loss. For example, the average sensorineural hearing loss in case 1 is 17.86 dBHL (250, 500, 1000, 2000, 3000, 4000, 8000 Hz) and case 2 is mixed. For hearing loss, the average decline in air conduction was 51.42 dBHL (250, 500, 1000, 2000, 3000, 4000, 8000 Hz), and the average decline in bone conduction was 30.71 dBHL (250, 500, 1000, 2000, 3000, 4000, 6000 Hz), case 3 was the affected ear with a sensorineural hearing loss of 7.85 dBHL. The amplitude of sensorineural hearing loss in case 4 was 24.28 dBHL (250, 500, 1000, 2000, 3000, 4000, 8000 Hz). Combining the MRI delayed scan results of 4 patients with Ramsay Hunt syndrome, it can be seen that the symptoms and signs of 4 patients may be mainly due to labyrinthine inflammation. Among them, case 1 has both vestibular neuritis; case 2 has both facial neuritis and otitis media, so there is also peripheral facial paralysis and mixed hearing loss; case 3 has both vestibular neuritis and cochlear neuritis, but vertigo and hearing loss not obvious; case 4 had vestibular neuritis, cochlear neuritis, facial neuritis, etc., so there was also peripheral facial paralysis. At the same time, these 4 cases of Ramsay Hunt syndrome labyrinthitis were finally cured after treatment, indicating that the labyrinth damage in these 4 cases of Ramsay Hunt syndrome labyrinthitis is all reversible.

In the otology clinic, sudden deafness and vertigo are common diseases, and it is often believed that viral infection may be one of the important causes of sudden deafness and vertigo. The 4 cases of Ramsay Hunt syndrome labyrinthitis, vestibular neuritis, cochlear neuritis, and facial neuritis are evident, but other viral infections do not produce typical skin lesions and pain symptoms like varicella-zoster virus infection, it is not easy to detect and make the corresponding clinical diagnosis with laboratory basis, so the etiological diagnosis of these sudden hearing loss and vertigo is often ignored.

In addition, as for the relationship between position perception, the severity of hearing impairment, frequency range, and the degree and range of high signal intensity of gadolinium enhancement, due to the apparent lack of cases in this article, cannot be clarified, and it needs to be discussed and explained in future using large sample cases.

In conclusion, by comparing the 3D-FAIR and T1VIBE sequences of the above 4 patients with Ramsay Hunt syndrome before intravenous gadolinium injection and after intravenous gadolinium injection with delayed 4.5-hour enhanced scans, it was found that (i) 3D-FLAIR sequence scanning with a delay of 4.5 hours is easier to show whether the permeability of the blood labyrinth barrier in the inner ear is increased. (ii) Ramsay Hunt syndrome deep ear tissue damage can be manifested as labyrinthitis, vestibulocochlear neuritis, facial neuritis, and otitis media.

Ethics Committee Approval: This study was approved by Ethics Committee of People's Hospital of Dongshneg District, Ordos City (Approval No: 2020-s001, Date: March 13, 2020).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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