ORIGINAL ARTICLE

Prognostic Value of Extension Patterns on Follow-up Magnetic Resonance Imaging in Patients With Necrotizing Otitis Externa

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Objectives: To analyze the clinical characteristics of necrotizing otitis externa (NOE) and to evaluate the prognosis according to the progression of disease in terms of extension patterns on follow-up magnetic resonance images.

Design: A retrospective clinical study.

Setting: Tertiary academic center.

Patients: We reviewed medical records of 36 patients with NOE followed up by temporal bone magnetic resonance images on a regular basis from January 1, 1992, through December 31, 2008.

Main Outcome Measures: The initial compartments affected by NOE were defined as 4 categories: anterior, medial, midline, and intracranial and extracranial. The extensions of NOE were evaluated by comparison between initial and follow-up magnetic resonance images 6 months later and defined by the direction of spread from one to another compartment and/or disease progression within the same compartment. The patients were divided into 3 groups (limited, single, and multiple extension groups) on the basis of the multiplicity of extension routes. The clinical characteristics and prognostic factors were investigated, and overall survival rates were compared according to extension patterns.

Results: Retrocondylar fat infiltration (86%) was the most common finding, followed by parapharyngeal fat infiltration (81%) and ipsilateral nasopharyngeal musculature thickening (75%). Anterior and medial extension patterns were observed in 3 (8%) and 5 (14%) patients, respectively. Eighteen patients (50%) with combined extension patterns showed a significantly lower overall survival rate than those with single and limited extension patterns ($P = .01$).

Conclusion: The retrocondylar fat infiltration was the earliest change in NOE, and combined extension patterns may be a poor prognostic factor in patients with NOE.

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NECROTIZING OTITIS EXterna (NOE) is a rare chronic progressive disorder that mainly affects elderly diabetic patients with high mortality. In 1968, Chandler[1] first reviewed 17 NOE cases and described their characteristics as old age, multiple cranial nerve palsies, and high mortality up to 53%. He also reported that *Pseudomonas aeruginosa* was the most common pathogen.

The extension patterns of NOE are diverse. After developing initially from the external auditory canal, it can spread anteriorly-inferiorly toward the parotid gland via the fissure of Santorini, anteriorly into the temporomandibular joint and masticator muscle, medially into the petrous apex via the middle ear, and contralaterally toward the other external auditory canal.[2] Some investigators have suggested that microangiopathy secondary to diabetes mellitus may decrease local blood flow, which results in a low concentration of antibiotics in target tissue.[3] However, the exact pathogenesis that explains the multidirectional extension is not yet elucidated.

Diagnosis of NOE is based on typical symptoms, signs, diverse laboratory findings (eg, elevated erythrocyte sedimentation rate, C-reactive protein, and cultures of organisms in ear discharge), and results from imaging studies. Previous studies have proven the superiority of magnetic resonance images (MRIs) to temporal bone computed tomography scans as an imaging modality to monitor the progression of disease in that MRIs provide much more information on not only anatomical extent of disease but also on bone marrow involvement and intracranial extension.[4] Despite these advantages, there are

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no widely accepted prognostic factors associated with MRI findings. Hence, the aims of this study were to analyze the initial MRI findings and extension patterns of NOE on follow-up MRIs and to obtain survival rates according to these parameters. The clinical characteristics and prognostic factors were also evaluated.

METHODS

We undertook a retrospective review of medical records of 45 patients who received a diagnosis of and treatment for NOE at the Department of Otorhinolaryngology in Seoul National University Hospital (Seoul, Korea) from January 1, 1992, through December 31, 2008. The study was approved by the institutional review board of the Clinical Research Institute in Seoul National University Hospital. Diagnostic criteria included symptoms such as otorrhea, otalgia, facial nerve palsy, and headache as well as typical involvement of the external auditory canal on the imaging studies, such as temporal bone computed tomography, MRI, and bone scintigraphy (gallium-67 scan).

Of 45 patients who were followed up by MRI on a regular basis, 36 were included in the study. The study group was composed of 27 men and 9 women, with an overall mean (range) age of 70 (51-97) years. The mean (range) duration of treatment was 9.6 (4-17) weeks, and the mean (range) follow-up period was 38 (6-120) months. The antibiotic therapy was administered intravenously in all cases. Most patients were treated with ceftazidime pentahydrate and monobactam series or ciprofloxacin hydrochloride. The treatments changed on the basis of susceptibility tests of antibiotics against pathogen on culture or on the basis of biopsy results. In the case of NEO due to methicillin-resistant *Staphylococcus aureus*, patients were treated with vancomycin or teicoplanin. In the event of NEO due to *Aspergillus* that was proven by culture or biopsy, patients were treated with amphotericin B. Surgical interventions were performed for drainage of abscesses, removal of sequestrum, or exclusion of neoplasm on 18 patients (50%) who showed poor responses 4 to 8 weeks after intravenous antibiotics treatment. Various surgical approaches were used: simple mastoidectomy, intact canal wall mastoidectomy, canal wall down mastoidectomy, subtotal petrosectomy, and the infratemporal fossa approach.

Pretreatment MRI was evaluated to identify the initial compartments affected by NOE. The authors subdivided and defined these compartments into 4 categories: anterior (retrocondylar fat, condylar bone marrow, temporomandibular joint, and masticator space), medial (nasopharyneal musculature, parapharygneal fat, and petrous apex), midline (clivus and preclival soft tissue), and intracranial and extracranial (middle and posterior fossa dura, spine, and neck) compartments. Areas with thickening and infiltration of soft tissue with high signal intensity were considered areas of disease involvement. Follow-up MRIs were obtained at intervals of 2 to 3 months for evaluation of the response to treatment. The extensions of NOE were evaluated by comparison between the initial and follow-up MRIs 6 months after initial treatment and were defined by the direction of spread from one to another compartment and/or disease progression within the same compartment. For instance, the anterior extension indicates that disease progressed from another compartment to the anterior compartment and/or within the anterior compartment. This classification was modified from the spreading patterns previously reported.[4] Patients were divided into 3 groups (limited, single, and multiple extension groups) on the basis of the multiplicity of extension routes. The single extension group was composed of the patients with progression of disease within the same compartments and with extension to a single compartment. The patients without any definite extensions were classified as the limited extension group. The patients who showed more than 1 extension pattern at the same time were allocated to the combined extension group.

The control of disease was defined as an improvement of clinical symptoms and radiologic findings on follow-up gallium-67 scans or MRIs. The overall survival rate was calculated using the Kaplan-Meier method and compared according to the extension patterns. The medical records on clinical characteristics, underlying medical conditions, involvement of the cranial nerves, culture of offending pathogens, and outcomes of surgical and medical therapy were also evaluated. Statistical analysis was performed using the χ^2 or Fisher exact test. The criterion for statistical significance was set at $P < .05$.

RESULTS

CLINICAL CHARACTERISTICS OF THE PATIENTS WITH NOE

Seventeen patients had left-side NOE and 14 had right-side NOE. The others had bilateral lesions (**Table 1**). Twenty-eight of 36 patients (78%) complained of severe otalgia and/or otorrhea. Twenty-seven patients had diabetes (75%), of whom 10 were insulin dependent. However, there was no difference in extension patterns ($P = .87$) and prognosis ($P = .09$) between insulin-dependent and non–insulin-dependent patients. The patients with NOE had a variety of underlying diseases, such as hypertension, cerebrovascular disease, active tuberculosis, angina, chronic renal failure, adrenal insufficiency, hyperthyroidism, hemato-oncologic malignant tumor, or solid tumor. Of the 36 patients, 17 had more than 2 underlying diseases. However, there was no significant correlation between the presence of multiple underlying diseases and the survival rate ($P = .09$). The most common pathogen was *P aeruginosa* (13 cases [36%]), followed by methicillin-resistant *S aureus* (8 [22%]) and *Aspergillus* species (5 [14%]). *Pseudomonas aeruginosa* was resistant to ciprofloxacin in 8 of the 13 cases (62%). In this study, 11 of 36 patients underwent the bone scan, and 4 patients underwent 2 to 3 serial scannings that showed active bone lesions in the skull base.

The most common cranial nerve involved at presentation was the facial nerve (7 cases [19%]). However, there was no significant correlation between facial nerve involvement and the survival rate ($P = .28$). Fifteen cases (42%) revealed multiple cranial nerve involvement, such as cranial nerves V, VI, VII, IX, X, and XII. The treatment outcome of all patients was as follows: 15 died of uncontrolled NOE, 5 died of unrelated causes, 8 had no evidence of NOE, and 8 were receiving regular follow-up because of incompletely controlled NOE. The overall mortality was 42% (15 of 36) in our study group. The clinical characteristics of all 36 patients are summarized in Table 1.

INITIAL FINDINGS OF NOE ON MRI

The retrocondylar fat (31 cases [86%]) in the anterior compartment was the most frequently involved subsite. The medial compartment was frequently involved: parapharyngeal space in 29 cases (81%) and the nasopha-

Table 1. Clinical Features of 36 Patients With Necrotizing Otitis Externa

Patient No./ Sex/Age, y	Side	Chief Complaints	Underlying Diseases	CN	Culture/ Biopsy	Initially Involved Compartment	Extension Pattern[a]	Surgery	Result
1/M/72	L	Otalgia/otorrhea	DM	IX	. . .	Ant, med	Ant	ITFA	NED
2/M/65	L	Otalgia/trismus	DM	. . .	. . .	Ant, med	Ant	. . .	AWD
3/M/70	R	Diplopia/facial palsy	DM	VI, VII	*Aspergillus*	Ant, med, intra	Ant	. . .	AWD
4/M/77	L	Otalgia/trismus	CVA Hx	VII, IX, X, XII	Pseudo/MRSA	Med	Med	. . .	DOD
5/M/64	L	Hoarseness/ dysphagia	. . .	VI, VII, X, XII	Pseudo	Med	Med	. . .	NED
6/M/59	B	Headache/dysarthria	DM, HT, Tbc HCC s/p TACE	VII, XII	Pseudo/MRSA	Med, mid	Med	. . .	NED
7/F/70	L	Headache/ hoarseness	DM, CRF	X	Pseudo	Ant, med, intra	Med	CD	NED
8/M/75	R	Dizziness/otorrhea	DM	. . .	. . .	Med	Med	. . .	DOD
9/F/64	L	Hoarseness	DM	IX, X, XII	. . .	Ant, med	Limited	SM	DOD
10/F/51	B	Facial palsy/vertigo	. . .	VII	MRSA	Med	Limited	ICW FND	AWD
11/M/56	B	Otalgia/otorrhea	. . .	. . .	. . .	Ant, med, intra	Limited	. . .	NED
12/M/69	R	Facial palsy/otalgia	DM, HT	III, IV, V, VI, VII, IX, X, XII	. . .	Ant, med, intra	Limited	. . .	DOD
13/F/56	R	Otorrhea	DM, asthma, parotid cancer	. . .	Pseudo	Intra	Limited	STP	NED
14/M/75	R	Facial palsy/otalgia	DM, HT	VII	Pseudo	Med	Limited	ICW FND	DOO
15/M/71	L	Otorrhea	DM, HT, CRF, CVA	. . .	Pseudo	Med, intra	Limited	. . .	DOO
16/F/65	R	Otalgia	. . .	. . .	Pseudo	Med, mid, intra	Limited	. . .	NED
17/M/74	L	Otalgia/otorrhea	DM	. . .	MRSA	Med, mid, intra	Limited	CD	AWD
18/M/85	R	Otalgia/otorrhea	HT	. . .	Pseudo	Med	Limited	. . .	AWD
19/M/71	B	Facial palsy/otalgia	HT	VII	. . .	Med, intra	Med, mid	. . .	NED
20/M/79	L	Dysarthria/otalgia	DM	IX, X, XII	*Aspergillus*	Med, mid	Med, mid	. . .	AWD
21/M/67	L	Headache/otalgia	DM	VI	*Rhodotorula glutinis* *Phchia ohmeri*	Med, mid	Med, mid	SM	DOD
22/F/73	R	Otalgia/hoarseness	. . .	IX, X	. . .	Ant, med	Med, ant, mid	. . .	AWD
23/M/68	R	Headache/facial palsy	DM, HT	VII	Pseudo	Ant, med, mid, intra	Med, ant	STP	DOO
24/M/72	R	Otalgia/trismus	DM, HT	. . .	MRSA	Ant, med, intra	Med, ant	. . .	DOO
25/M/55	L	Otalgia/otorrhea	DM, 3-vessel disease	VII	MRSA	Ant, med	Med, ant	. . .	DOO
26/F/61	R	Otalgia/headache	DM	. . .	Pseudo	Ant, med, mid	Med, ant, mid	SM	AWD
27/F/82	R	Otalgia/otorrhea	HT	VII, IX, X, XII	Pseudo/MRSA	Med, intra	Med, mid	. . .	DOD
28/M/72	L	Otalgia/facial palsy	DM CRF	VII, X, XII	. . .	Ant, med, intra	Med, ant, mid	ITFA with STP	DOD
29/M/72	B	Otalgia/otorrhea	DM, HT	VII, IX, X	MRSA	Ant, med, intra	Med, ant	. . .	DOD
30/M/97	L	Otalgia/otorrhea	DM, HT	. . .	Pseudo	Ant, med	Med, ant, mid	ICW	DOD
31/M/64	L	Otalgia	DM	. . .	. . .	Ant, med	Med, ant, intra	ICW →ITFA with STP	DOD
32/M/70	R	Otalgia	DM, angina	VII	*Aspergillus*	Ant, med	Med, ant, intra	SM →ICW with FND	DOD
33/M/51	R	Headache	DM triopathy, HT	VI, VII	*Aspergillus*	Ant, med, mid, intra	Med, extra	ICW→ITFA	DOD
34/F/72	L	Headache/otorrhea	DM, HT	. . .	. . .	Med, intra	Med, intra	. . .	DOD
35/F/72	L	Otorrhea/otalgia	DM, rectal Ca s/p chemoTx, VZV infection	VII, XII	*Aspergillus*	Ant, med, intra	Med, intra	STP brain abscess removal	DOD
36/M/66	L	Otalgia/otorrhea	DM adrenal insufficiency	VI, VII, IX, X, XII	. . .	Med, mid, intra	Med, Extra	. . .	DOD

Abbreviations: ant, anterior; AWD, alive with disease; B, bilateral; Ca, cancer; CD, canal wall down mastoidectomy; chemo, chemotherapy; CN, cranial nerve; CRF, chronic renal failure; CVA, cerebrovascular accident; DM, diabetes mellitus; DOD, died of disease; DOO, died of other cause; extra, extracranial extension; FND, facial nerve decompression; HCC, hepatocellular carcinoma; HT, hypertension; Hx, medical history; ICW, intact canal wall mastoidectomy; intra, intracranial extension; ITFA, infratemporal fossa approach; L, left; med, medial; mid, midline; MRSA, methicillin-resistant *Staphylococcus aureus*; NED, no evidence of disease; Pseudo, *Pseudomonas aeruginosa*; R, right; SM, simple mastoidectomy; s/p, solved problem; STP, subtotal petrosectomy; TACE, transarterial chemoembolization; Tbc, tuberculosis; Tx, treatment; VZV, varicellar-zoster virus.

[a] The extension patterns were defined as spreading from one to another compartment or disease progression within the same compartment. The patients without any definite extension were classified as the limited extension group.

ryngeal musculature in 27 cases (75%) (**Table 2**). The preclival soft tissue was the most common area of involvement among the midline compartment. Seven patients (19%) showed contralateral preclival soft-tissue enhancement, and 15 patients (42%) had dural enhancement at the time of initial presentation.

Table 2. Subsites of Initially Involved Compartment on Magnetic Resonance Imaging for 36 Patients

Compartment	Subsite	No. (%)
Anterior	Retrocondylar fat	31 (86)
	Condylar bone marrow	21 (58)
	Temporomandibular joint/masticator space	18 (50)
Medial	Parapharyngeal fat	29 (81)
	Nasopharyngeal musculature thickening	27 (75)
	Petrous apex	20 (56)
Midline	Preclival soft tissue	24 (67)
	Clivus	21 (58)
	Contralateral preclival soft tissue	7 (19)
	Contralateral nasopharyngeal musculature thickening	5 (14)
Intracranial and extracranial	Middle and posterior fossa dural enhancement	15 (42)

Table 3. Extension Pattern in 36 Patients

Extension	No. (%)
Single extension	8 (22)
Anterior	3 (8)
Medial	5 (14)
Limited	10 (28)
Combined extension	18 (50)
Medial, midline	4 (11)
Medial, anterior	4 (11)
Medial, anterior, midline	4 (11)
Medial, anterior, intracranial	2 (6)
Medial, extracranial	2 (6)
Medial, intracranial	2 (6)

EXTENSION PATTERN ON FOLLOW-UP MRI

The patients were divided into the single/limited and combined extension group on the basis of the multiplicity of extension routes (Table 1 and **Table 3**). Anterior and medial extension in the single extension group were observed in 3 (8%) and 5 (14%) patients, respectively. There was no definite extension of the disease on follow-up MRIs in 10 patients (28%; the limited group). Eighteen of 36 patients (50%) showed combined extension patterns. Medial extension was uniformly observed in all the patients in the combined extension group. Simple illustrative cases are shown in **Figure 1** and **Figure 2**.

CLINICAL OUTCOMES ACCORDING TO EXTENSION PATTERN

The anterior extension group had no deaths among its 3 patients, whereas mortality in the medial group was 40% (2 of 5 patients) and in the limited extension group was 20% (2 of 10 patients). The overall mortality of the single/limited extension group due to disease was 22% (4 of 18 patients). On the other hand, the combined extension group showed a mortality of 61% (11 of 18 patients), which was significantly higher than that of the single/limited extension group (Table 1). Three of 5 patients with *Aspergillus* infection in the combined extension group died irrespective of the extension pattern, whereas 1 patient with *Aspergillus* species in the combined and 1 patient in the single extension group survived with disease.

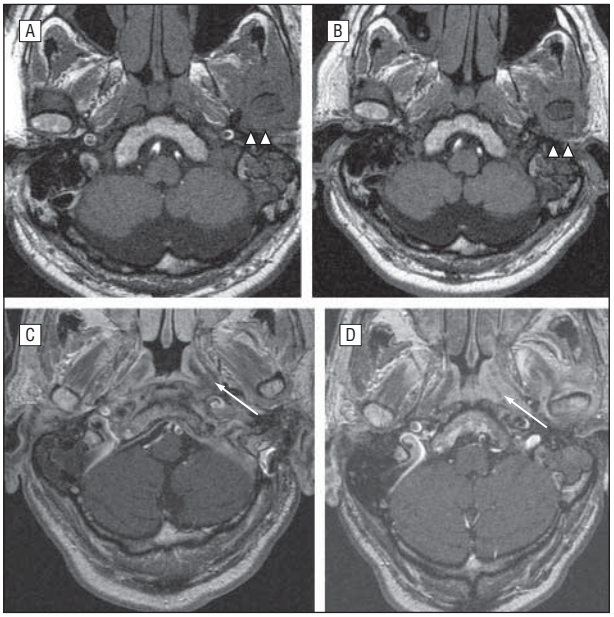

Figure 1. Illustrated cases of the single extensions: anterior (A and B, T1-weighted) and medial (C and D, T1-enhanced) extension. Retrocondylar space involvement (A, arrowheads) and nasopharyngeal musculature thickening (C, arrow) aggravated on 6-month follow-up scans (B and D), respectively.

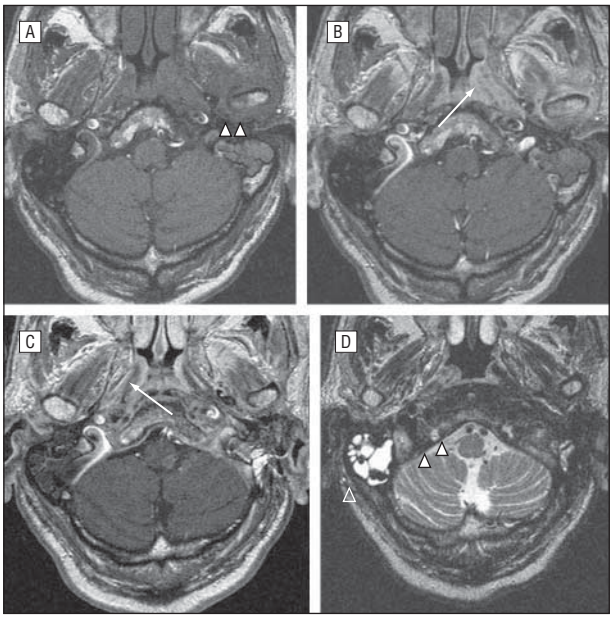

Figure 2. An illustrated case of the combined extension. Retrocondylar space widening (A, arrowheads, T1-weighted) and left nasopharyngeal musculature thickening (B, arrow, T1-enhanced). Six months later, right nasopharyngeal musculature thickening (C, arrow, T1-enhanced) and skull base infiltration (solid arrowhead) and mastoid effusion (open arrowhead) (D, T2-weighted).

Survival rates according to the multiplicity of extensions are shown in **Figure 3**. The relationship between longitudinal survival rates of the 2 groups and several factors, such as involvement of the cranial nerves at presentation, coexistence of underlying medical problems, and surgical intervention, were also evaluated. How-

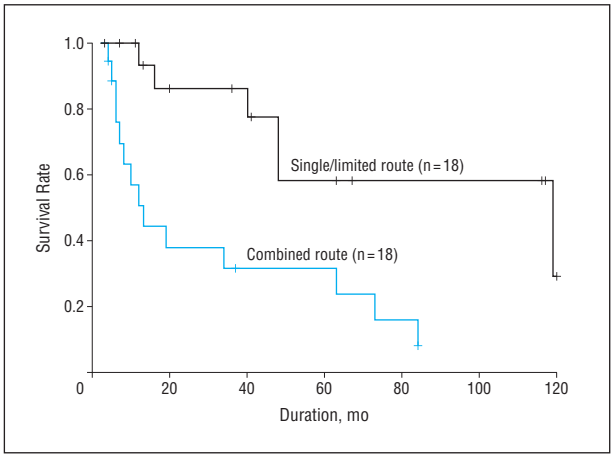

Figure 3. Survival rates according to the multiplicity of extension patterns. The combined extension group showed a poorer survival rate than the single/limited extension group.

ever, these factors had no significant correlations with the survival rate.

COMMENT

The clinical characteristics found in this study were similar to those in the previous studies. Considering that diabetes deteriorates the ability to control the infection, it is important to decrease blood glucose level strictly.[5] In this study, 27 patients (75%) had diabetes, which was insulin dependent in 10. However, it did not significantly affect prognosis. The most commonly involved cranial nerve was facial nerve VII, followed by X, XII, and IX. The existence of facial palsy at the time of diagnosis was not associated with prognosis, which was in line with the previous studies.[6,7] Two of 5 patients with *Aspergillus* were considered initially infected with *Aspergillus* on the basis of the biopsy performed immediately after admission. In 3 of 5 patients, it is hard to determine whether the infection was caused by long-term antibiotic treatment, but it is conceivable that NOE in these patients might be due to this reason. There was no fungal disease identified in other parts of the body in these patients.[8] Our results showed an overall mortality of 42%, which was similar to those of previous reports (0%-53%).[1,4,6,9,10]

Several imaging modalities have been suggested to evaluate disease progression and prognosis in patients with NOE. Before the introduction of computed tomography and MRI, radionuclide scanning or pluridirectional tomography were the modalities of choice for detection and evaluation of NOE. Later, the technetium-99m and gallium-67 citrate scans were suggested as the most accurate methods for the early detection and follow-up of NOE.[3] In addition, gallium-67 citrate scans were reported to correlate well with clinical resolution of NOE as the clinical status of patients improved.[2] However, this method has drawbacks, such as ambiguous localization and low specificity.

An imaging modality for NOE should enable the physician to delineate the exact extent of the infection both in bone and soft tissue. Computed tomography scans are superior to MRIs in detecting early cortical bony changes, which are not definable by MRIs. However, because remineralization of the eroded bone takes a long time, regression of disease cannot be accurately assessed by computed tomography scans. In contrast, MRIs have noticeable advantages in evaluating the dural enhancement and detecting changes in the medullary space of bone.[2]

Although many centers perform follow-up MRI repeatedly to evaluate extension of the disease and therapeutic effect of NOE, there have been few studies on the prognostic predictability of MRIs. Several recent reports have pointed out some important findings on MRIs that were related to the prognosis of NOE. The use of nasopharyngeal involvement on computed tomography scans or MRIs as a prognostic factor was reported previously.[9] In that study, nasopharyngeal musculature was considered one of the routes for disease progress in the multiple extension group. Kwon et al[4] reported that the presence of an abnormal flow void and intracranial dural enhancement on MRI may indicate a poor prognosis. They also stated that retrocondylar fat infiltration is always present in patients with NOE. As to the prognosis of the anterior extension of NOE, there have been 2 conflicting reports.[4,11] Mardinger et al[11] reported a mortality of 50% in patients with NOE and an extension toward the temporomandibular joint area. In contrast, Kwon et al found no difference in the frequency of anterior extension between the patients with good and those with poor outcomes.

In this study, 86% of the patients showed retrocondylar fat infiltration, which was the most common subsite involved initially (Table 2). Also, most cases involved the medial compartment initially. Therefore, when NOE is suspected, physicians should check the retrocondylar subsite and medial compartment first to support the diagnosis. The present study revealed a control rate of 100% (3 of 3 patients) in the patients with anterior extension. Compared with that of the other extension patterns, the relatively low possibility of invasion of the critical structures, such as the cranial nerves and major blood vessels, may explain the good prognosis of the patients with anterior extensions. On the other hand, the mortality of the patients with medial extensions was 40% (2 of 5 patients), which was the highest among the single/limited extension groups. All patients in the combined extension group had medial extensions in common, and their mortality was 61% (11 of 18 patients). The involvement of the medial compartment seems to be responsible for multiple cranial nerve palsies shown in 14 patients. Hence, medial extension may be regarded as an ominous prognostic factor.

Survival rates according to each single extension pattern showed no statistically significant difference. However, patients in the combined extension group showed significantly shorter survival than those in the single/limited extension group. The overall mortality was 42% (15 of 36 patients), which may be attributable to the fact that our hospital is a tertiary referral center. Most patients enrolled in the present study were transferred from other hospitals with delayed or incorrect diagnosis or recalcitrance to the treatment. Most patients presented with poor general condition or resistance to systemic antibiotic therapy.

In conclusion, because the involvement of the retrocondylar fat (86%) was the most common finding of NOE, physicians need to check the anterior compartment first on MRI when NOE is suspected clinically. Also, many cases of NOE extended as combined patterns (50%) on follow-up MRIs showed much poorer survival than the patients in the single/limited extension group. Therefore, MRI follow-up on a regular basis in patients with NOE is recommended because it provides diagnostic and prognostic values.

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