Malignant otitis externa: experience with hyperbaric oxygen therapy

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Key words
Hyperbaric oxygen therapy, malignant otitis externa, ENT, clinical audit, outcome

Abstract
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Introduction: The treatment of malignant otitis externa (MOE) with hyperbaric oxygen therapy (HBOT) remains controversial. The rarity of MOE, combined with poor access to hyperbaric facilities, explains the paucity of existing data.
Methods: We retrospectively reviewed all patients with a diagnosis of MOE referred to the Prince of Wales Hospital hyperbaric unit over a period of six years, and report one of the largest case series to date.
Results: From August 2001 to October 2007, 17 patients with MOE were referred, of whom 15 (88%) completed therapy, one did not tolerate HBOT and one was withdrawn due to pulmonary complications. Length of admission averaged 48 days (range 8–93 days) and three received outpatient care. Five patients had complications attributable to HBOT: acute pulmonary oedema (n = 2), seizure (n = 1), tympanic membrane perforation (n = 1) and claustrophobia (n = 1). Average time to follow up was 47 months (range 1–94 months). Twelve patients (70%) were considered cured of their disease, being disease-free at follow up, including four patients who had died of other causes but were symptom-free at the time of death. Three patients died directly from MOE (18%), one after a recurrence of their disease. Two further patients had recurrent disease, both successfully treated with a second cycle of HBOT and antibiotics. Nine patients (53%) had facial nerve palsy before commencement of HBOT, of whom four died, three from MOE, four had ongoing facial paralysis, and one resolved.
Conclusions: HBOT confers minimal morbidity, but its role in MOE remains uncertain. The high mortality of MOE despite maximal therapeutic intervention highlights the need for more effective treatment protocols.

Introduction

Malignant otitis externa (MOE) refers to a severe infection involving both the external auditory canal and the surrounding skull base (temporal, occipital or sphenoid bones).[1] MOE usually arises secondary to inadequately treated chronic otitis externa, although it may also originate from chronic otitis media, sphenoid sinusitis or any inadequately treated infection in close proximity to the skull base.[1] Previous series have found the most common causative agent to be *Pseudomonas aeruginosa*.[2]

Afflicted patients generally tend to be elderly and have some form of systemic immunocompromise, most often diabetes mellitus, or a history of radiotherapy for a head and neck malignancy in the region of the skull base.[3] Patients frequently present with vague symptoms running a long and insidious course. More severe symptoms include unilateral severe otalgia of prolonged duration and out of proportion for routine external otitis, unremitting headache mainly over the temporal and parietal regions, recurrent and relapsing otorrhoea, hearing impairment, vertigo and a sensation of aural fullness.

Treatment protocols for MOE are controversial but usually include long periods of both intravenous and subsequent oral antibiotics with various adjuvant therapies including antifungal medications, surgical debridement and hyperbaric oxygen therapy (HBOT).[4–12] A typical protocol for HBOT is 90–100 minutes daily at between 203 and 243 kPa repeated 20 to 60 times.[8,12–14]

Since 2001 the department of Otolaryngology, Head and Neck Surgery at Prince of Wales Hospital in Sydney has routinely referred patients with established MOE for consideration of HBOT and this case series documents our experience to date.

Materials and methods

Following approval from the South East Sydney Health Area (Northern Network) Human Research Ethics Committee (ref: 07/07), we conducted a retrospective review of all patients who had received HBOT at the Prince of Wales Hospital Department of Diving and Hyperbaric Medicine (DDHM) to treat MOE. Long-term outcomes were determined by chart review, patient assessment and telephone interview.

We identified suitable cases by examination of the DDHM database (FileMaker Pro 5.1, FileMaker Inc, 1999) using 'acute necrotising infections', 'osteomyelitis', 'other infections' and 'audiovestibular' as non-exclusive search terms. Where insufficient information was available on the database, we retrieved the full medical record and conducted a telephone interview with the patient or a relative as appropriate. All facial nerve palsies were graded on the House Brackman system from II (slight) to VI (total).[15]

Table 1
Summary table of 17 patients, pathogens grown and treatment outcomes; MRSA – Methicillin-resistant *Staphylococcus aureus*; MOE – malignant otitis externa; HBOT – hyperbaric oxygen therapy; TM – tympanic membrane; o/p – out-patient

Patient	Age/sex	Diabetes	Cranial neuropathy	Pathogen	Admission (days)	HBOT (number)	HBOT problem	Outcome	Follow up (months)
1	75 M	Yes	No	*Bacteroides*	53	29		Ongoing otorrhoea, died of other disease	62
2	79 M	No	No	MRSA	32	30		Disease free, died of other disease	90
3	72 M	Yes	VII	*P. aeruginosa*, *Candida* spp	36	30		Disease free, ongoing VII palsy	51
4	81 M	No	No	Unspecified yeast	57	30		Disease free	37
5	66 M	Yes	VII	Negative cultures	59	40		Died of MOE (2 months)	2
6	65 F	Yes	VII	*P. aeruginosa*, *S. aureus*	71	37		Seizure, died of MOE (1 month)	1
7	84 M	Yes	VII	Negative cultures	17	5	Pulmonary oedema	Disease free, VII palsy resolved	72
8	78 M	Yes	XII	*P. aeruginosa*	45	30		Disease free, XII palsy resolved	94
9	65 M	Yes	No	Negative cultures	8	1	Claustrophobia	Otorrhoea and otalgia	80
10	71 F	No	No	Negative cultures	o/p	30		Disease free, died of other disease	26
11	75 F	No	No	*P. aeruginosa*	9+o/p	30		Disease free, died of other disease	38
12	84 M	Yes	VII	*P. aeruginosa*, *S. aureus*	43	29	Perforated TM	Recurrence (11 m), VII palsy, died of other disease	37
13	69 M	Yes	No	*S. epidermidis*, *S. apiospermum*	42	30		Disease free	43
14	76 M	Yes	VII	*P. aeruginosa*, *Candida spp*	o/p	30		Disease free, ongoing VII palsy	49
15	71 M	Yes	VII (X)	*P. aeruginosa*, *Candida* spp *S. apiospermum*	74	39		Recurrence (4 m), new X palsy, died of MOE	6
16	77 F	Yes	VII, IX, XII	*P. aeruginosa*	39	30	Pulmonary oedema	Disease free, ongoing VII palsy, IX & XII resolved	77
17	77 M	Yes	VII	MRSA, *Corynebacterium*, *Aspergillus flavus*	93	38		Recurrence (5 weeks), disease free, ongoing VII palsy	35

Results

Between August 2001 and October 2007, 17 patients were accepted for HBOT therapy for confirmed MOE (Table 1). The average age was 75 years (range 65–84 years), and there were 13 males. Eight cases involved the right ear alone, eight the left and one patient had bilateral disease. A complete course of HBOT was achieved in 15 of the 17 patients (88%). Those who underwent a complete course had between 29 and 40 treatment sessions, with a median of 34.

All patients received broad-spectrum and culture-directed intravenous or oral antibiotics under the direction of the infectious diseases department. The area was debrided surgically as clinically indicated or based on imaging evidence. All but two patients were treated as in-patients, depending on their physical ability. Diagnostic and progress imaging was undertaken as clinically necessary.

All patients were treated in a multiplace chamber once daily from Monday to Friday on a standard 90-minutes schedule at

243 kPa breathing 100% oxygen. All patients were initially scheduled to receive 30 sessions over six weeks, but this course could be shortened or extended depending on the clinical and/or imaging response.

The average duration of symptoms prior to presentation at POWH was 4 weeks (range 2–6 weeks). The most common symptom was otalgia (94%), followed by otorrhoea (75%), headache (50%), facial or jaw pain (19%) and tinnitus (13%). Examination revealed the typical findings associated with otitis externa, including purulent discharge in the external auditory canal and tenderness on manipulation of the pinna. Only two patients were febrile on admission. Nine patients (53%) had a facial nerve palsy on admission with documented grading of House Brackman IV in one case, V in another and 'abnormal' in the remainder. Involvement of other cranial nerves was rare. Two patients had hypoglossal neuropathy, one of whom had additional glossopharyngeal nerve involvement.

Thirteen patients (76%) had a previous diagnosis of type II diabetes mellitus, of whom three were insulin-dependent. The average HbA1C at the time of diagnosis of MOE was 7.0%. Other co-morbidities included ischaemic heart disease ($n = 7$), chronic renal failure ($n = 2$), alcoholic liver cirrhosis ($n = 1$) and one patient who had undergone successful renal transplantation and was immunosupressed. Three patients had a history of previous ear surgery temporally unrelated to the current infection; modified radical mastoidectomy in two and tympanoplasty in one. Eleven patients had a history of cigarette usage but only four were currently smoking. Four patients had significant regular alcohol intake.

INVESTIGATIONS

Imaging

All patients were investigated with a computed tomogram (CT) scan of the petrous temporal bones and Gallium 67 scintigraphy. Four patients had magnetic resonance imaging (MRI) of the area.

Microbiology

A pathogen was isolated in thirteen cases (76%). *Pseudomonas aeruginosa* was cultured in nine (56%), multiple pathogens in eight cases (47%) and fungal cultures were positive in six cases (35%). Table 1 details the microbiology.

TREATMENT

Three patients received HBOT as outpatients (two for the entire course, one after nine in-patient sessions). The remaining patients required admission either because of their health status or because they were geographically removed from their usual residence. Admission periods ranged from 8 to 93 days with an average of 48 days.

A variety of different antibiotic regimens were employed with varying time courses. The most common intravenous antibiotic was timentin, used in thirteen cases (76%). Systemic and ototopical ciprofloxacillin were also frequently prescribed. A systemic antifungal agent was added in four cases. On discharge, all patients received oral ciprofloxacillin, with or without ototopical drops, for an average of four months (range 1–9 months). In addition, culture-directed antibiotics were prescribed; oral flucloxacillin (two patients) and oral clindamycin, oral augmentin, oral voriconazole and IV timentin via a long line, each in a single patient.

In two cases, microscopic and diagnostic evaluation under general anesthesia with curette debridement of necrotic tissue in the external auditory canal was undertaken within the first few days of presentation. Histology demonstrated granulation tissue with necrosis and evidence of acute inflammation consistent with MOE. Two further patients underwent cortical mastoidectomy, one in conjunction with external ear canal debridement (prior to HBOT), and in the other, mastoidectomy was undertaken at the time of MOE recurrence (after HBOT).

ADVERSE EFFECTS

In addition to the cranial neuropathies described above, two patients had disease-related complications: sigmoid sinus thrombosis in one and temporomandibular joint septic arthritis requiring aspiration in another. One other patient developed a brachial vein thrombosis associated with antibiotic administration. No long-term sequelae from these complications ensued.

Complications that might be attributable to HBOT were encountered in five patients (29%): acute pulmonary oedema in two and seizure, tympanic membrane perforation and claustrophobia, each in a single patient. HBOT was stopped early in the course of two patients. One refused further sessions after the first, due to claustrophobia in the chamber, and the second was withdrawn due to worsening lung function following an episode of acute pulmonary oedema during the fifth HBOT on a background of chronic obstructive pulmonary disease. No long-term sequelae associated with these events occurred.

DISEASE PROGRESSION AND OUTCOME

Routine blood tests including white cell count (WCC), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were used in an attempt to monitor disease progression. WCC was almost entirely within the normal range throughout every patient's admission. A sustained moderate rise in CRP was found in most patients with little fluctuation as treatment progressed. ESR was more indicative of disease progression and trended down during the first month of HBOT in most patients.

All patients were followed up to June 2010. The average time of follow up was 47 months from diagnosis (range 1–94 months). Twelve patients (70%) were considered cured of their disease, being disease-free at follow up, including four patients who had died of other causes but were symptom-free for MOE at the time of death. Two patients died within two months of diagnosis despite a full course of HBOT and antibiotics and a third despite a second course of antibiotics and HBOT for a recurrence after four symptom-free months. Three patients had a recurrence of MOE; one died as outlined above. The second recurred at 11 months, and was successfully treated with a second course of antibiotics and HBOT. He died of an unrelated illness 26 months later, symptom-free for MOE. The third was readmitted only five weeks after discharge from hospital, with a new onset of facial nerve palsy. He went on to have a cortical mastoidectomy and commencement of systemic antifungal therapy after which he has remained disease free for 35 months.

Of the nine patients to have facial nerve involvement, four died, three from MOE, four had ongoing facial paralysis, and only one resolved. The one resolution occurred within one year after discharge. All lower cranial nerve neuropathies resolved during the time the patient was in hospital.

Discussion

The use of HBOT for MOE was first described by Mader in 1982 in a single case report.[9] Subsequently a number of case series have been reported (Table 2) but no randomised, controlled trials (RCTs) have been undertaken. Given the rarity of the disease and its variable presentation, this is not surprising.[12]

The treatment of MOE remains a formidable challenge despite improvements in antibiotic choice and increasing availability of new therapies such as HBOT. With the absence of RCTs studying the benefit of any therapeutic measures, including HBOT, we must rely on lower levels of evidence to guide the choice of therapy. At the present time with regard to HBOT, case series such as this are the best evidence we have upon which to base decisions. The rarity of MOE coupled with the relative paucity of available HBOT facilities makes this report an important summary of how MOE is treated in a tertiary referral centre with HBOT capabilities. The study size is one of the largest published (Table 2).[6–10,16–19]

Table 2
Published reports on hyperbaric oxygen therapy to treat malignant otitis externa; NR – not reported

Year	Author	Patients	Cure Rate
Case series			
1982	Lucente[17]	3	NR
1989	Shupak[7]	2	100 %
1992	Davis[6]	16	100 %
2004	Narozny[10]	8	88 %
2010	Present study	17	70 %
Case reports			
1982	Mader[9]	1	Cured
1990	Schweitzer[8]	1	Cured
1998	Bath[18]	1	Cured
2000	Lancaster[19]	1	Died
2005	Singh[16]	1	Cured

Pseudomonas remains the commonest pathogen, isolated in half our cases. However, multiple pathogens were cultured in a number of patients and nearly a third of patients had evidence of fungi present. Antibiotic choice should be culture-directed but, in the absence of positive cultures, a reasonable choice would be IV timentin combined with oral and topical ciprofloxacillin. An antifungal agent should be added if there are any features suggestive of fungal involvement.

The role of surgical debridement in the treatment of MOE remains controversial. A small proportion of patients in this series had surgical debridement of necrotic tissue. In terms of outcome, there is no clear evidence that debridement improves cure rate, cranial nerve palsy resolution or speed of recovery. In our series, both patients who underwent debridement were symptom-free at over a year of follow up with no recurrence, but neither had a resolution of their facial nerve palsy. Their length of stay was not significantly different from those who did not undergo surgery (37 versus 42 days respectively). With such small patient numbers, no solid conclusions can be drawn in regards to these findings. In our opinion, surgical debridement should be reserved for selected patients with disease progression despite maximal medical management and HBOT.

The mortality rate due to MOE in this series was 3/17 (18%). Previous case series involving the use of HBOT have reported mortality rates as low as zero and up to 12%.[6,11] On the other hand, Chandler described a rate of around a third in a series of 22 patients, only four of whom received HBOT.[2] Within our series, two-thirds of the patients were symptom-free at follow up. The part that HBOT played in such recoveries is hard to quantify. An argument against the use of HBOT would be that the one patient who withdrew from HBOT due to a complication made a full recovery including facial palsy resolution whilst three other patients succumbed to their disease despite a full HBOT course. In the group of patients with ongoing symptoms including otalgia and otorrhoea, and in the three patients who had recurrence, there were no obvious reasons for treatment failure. Their presentations and management protocols were not appreciably different from any of the disease-free group. The incidence of recurrence in the absence of HBOT with antibiotic therapy alone is reported to be in the order of 15–20%, so the finding of three cases in the 17 presented (18%) is within expectations.[16]

In this series the facial nerve was the most common cranial nerve to be involved, and was the least likely to resolve with treatment. Seven of nine patients presenting with a facial nerve palsy and who survived the disease had ongoing facial paralysis at long-term follow up (mean of 53 months in this subgroup). Involvement of the lower cranial nerves was rare. The journey of the facial nerve directly through the infected temporal bone as opposed to the paths of the lower cranial nerves which merely pass adjacent to the area affected by osteomyelitis is likely to be the explanation for this difference. Previous studies without HBOT have described a grave prognosis if lower cranial nerves are involved with mortality rates of 80–100%.[20] We did not find this, and the two patients with lower cranial neuropathies on their first presentation responded well to treatment, with complete resolution by the time of discharge from hospital. One patient who developed a tenth cranial neuropathy during a recurrence of his MOE did ultimately die. This suggests the development of lower cranial neuropathies later in the disease progression may be more significant than in the early stages of treatment.

The potential benefits of HBOT must be weighed against the associated complications. In our series almost one in three patients encountered some form of morbidity attributable to HBOT, which is contrary to the experience of previous authors.[6] Whilst the majority of problems, such as middle ear barotrauma, were relatively minor and did not preclude further therapy, a small proportion of patients did have significant problems with longer-term implications. Complications such as oxygen toxic seizures and acute pulmonary oedema are directly related to high intra-arterial oxygen tensions, and are well documented in the literature.[8,14] A recent review of 240 patients receiving a combined total of 4,638 HBOT sessions reported a complication rate of 20% of which 94% were 'mild to moderate'.[18] The incidence of serious complications including seizures and pulmonary oedema was 1.7% and there were no deaths.[21] In our series, one patient had to be withdrawn from further HBOT due to exacerbation of pre-existing chest disease. The other occurrence of pulmonary oedema was after the thirteenth treatment and resolved with diuretic therapy alone. The patient with HBOT-related seizures experienced these around 30 minutes into the first two sessions. Her blood sugars at the time of the seizures were recorded as 2.3 and 2.8 mmol L^{-1} respectively and resolved with injection of 50% glucose. Following a change to the protocol, incorporating two air breaks and an alteration to her insulin dose prior to commencing each session, she completed a full course of HBOT with no further complications.

It is interesting that, within the same institution, the treatment protocol for the 17 patients presented was different in every case, whether it be through antibiotic choice, length of treatment or number of HBOT sessions. Precise treatment protocols will always be tailored to specific patient need; however, a more unified approach to treating this disease is warranted. How to decide on such 'best practice' is more challenging. Access to hyperbaric facilities will always be relatively difficult, however, most countries have referral centres available and, given the rarity of this disorder, it seems appropriate that such cases are treated at a tertiary referral centre with a more unified approach.

Conclusion

Further research is required to fully understand the advantages, if any, HBOT offers patients with MOE. Our experience suggests HBOT, where available, is an appropriate adjunct to antibiotic regimens, with only minor associated morbidity. Despite this, a proportion of patients will succumb to their disease, which highlights the need to search for more effective treatment protocols.

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