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Otogenic brain complications: a systematic review and meta-analysis

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Abstract

Objective. This study aimed to form astute deductions regarding the presentation, treatment and mortality of otogenic brain complications.

Methods. A systematic literature search of four medical databases (PubMed, Embase, Web of Science and Scopus) was conducted. Studies associated with otogenic brain complications were considered eligible. Fixed- and random-effects model meta-analysis was developed to assess the proportion estimate for each outcome individually.

Results. Twenty-eight studies, with 1650 patients in total, were included. In 66 per cent of patients there was a known history of chronic otitis media. The most common symptoms were purulent otorrhoea (84 per cent), headache (65 per cent) and otalgia (45 per cent). A brain abscess was observed in 49 per cent of patients, followed by meningitis (34 per cent) and sinus thrombosis (22 per cent). A combination of surgical and conservative therapy was chosen in 84.3 per cent of cases and the mortality rate approached 11.1 per cent.

Conclusion. Otogenic brain complications are a possibly life-threatening condition. Prompt imaging examination may set the final diagnosis and lead to an effective treatment.

Main Article

Eleni Gkrinia takes responsibility for the integrity of the content of the paper

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Introduction

Otitis media is a common otological condition, defined as an acute or chronic infection of the middle ear, that affects both paediatric and adult populations.[1] Acute mastoiditis occurs consequently to otitis media with or without cholesteatoma and is a suppurative inflammation of the mastoid air cells lasting up to four weeks.[2,3] Even though the incidence of suppurative otitis media has been reduced due to progress in immunisation and antibiotic treatment, the anatomical proximity of the middle ear to the mastoid process and the temporal lobe allows for extension of the inflammatory process to the cardinal structures of the skull, leading to severe and perhaps deadly intracranial complications.[3,4]

Otogenic brain complications comprise meningitis, cerebral and cerebellar abscesses, and cerebral venous sinus thrombosis.[2] Symptomatology indicative of intracranial complications following otitis media is diverse and includes a variety of neurological clinical features such as headache, dizziness, nausea and diminished Glasgow Coma Scale scores.[5,6] Symptoms can also manifest with focal neurological deficits including meningism, paresis of cranial nerves, plegia, seizures, visual and acoustic disturbances, speech or balance impairment and fever.[6–8] The standard diagnostic algorithm is multidisciplinary and involves radiological investigation with computed tomography (CT) and magnetic resonance imaging (MRI) scans, laboratory analysis of cultures, and performing a standard neurological and otolaryngological clinical assessment.[9,10]

An overview of the available literature on otogenic brain complications points towards the lack of a well-established treatment algorithm. The treatment consensus consists of either solely conservative or, preferably, a combination of surgical management and administration of antibiotic regimen. Surgical procedures are performed by an otological surgeon or a neurosurgeon, either separately or combined.[3,4,11] Even if there is a punctual diagnosis and treatment initiation, the resolution of otogenic brain complications cannot always ensure complete recovery. There are reports on complications and mortality registered throughout the current literature, including cranial nerve palsies, epilepsy, dysphasia, hearing loss.[2,7]

Although rare in developed countries, otogenic brain complications still occur as a severe and potentially deadly medical entity. Because of the nature and scarceness of the disease, there have only been a few relevant large-scale studies and no randomised ones. The objective of the present study was to systematically review the existing evidence regarding the prevalence, presentation, microbiology, treatment options, morbidity and mortality rates of otogenic brain complications, as well as to perform a meta-analysis of the collected data, to deduce reliable conclusions concerning the optimal diagnostic and management modalities in view of determining the best possible final results.

Table 1. Search strategy

Frame	Mesh terms	Search	Inclusion criteria	Exclusion criteria	Sources
P (patients, participants, population)	1 'Otologic brain complications' OR 'otologic brain abscess' OR 'otologic cerebral abscess' OR 'otologic brain infection' OR 'otologic cerebral infection' OR 'otologic brain suppuration' OR 'otologic cerebral suppuration'	1 AND 2 AND 3 AND 4	Articles focusing on the management of ntological brain complications and their outcomes	Irrelevant title or abstract Irrelevant full text Not English Editorial, reviews, meta-analyses Studies with fewer than five subjects Experimental/ non-human studies Studies including exclusively paediatric populations Complications other than intracranial Indications other than otological infections Total number in patient sample not obvious Studies on revision cases	Databases (PubMed, Embase, Web of Science, Scopus)
I (intervention)	2 'surgical treatment' OR 'surgical management'				
C (reference test)	3 'conservative treatment' OR 'conservative management'				
O (outcome)	4 'symptoms' OR 'bacteriology' OR 'morbidity' OR 'mortality'				
Time	No limitations in terms of publication date Last search: April 2023				
Study design	Systematic review and meta-analysis				

Materials and methods

Search strategy

We prospectively designed the search methods, eligibility criteria and data extraction process. The patients' informed consent or Institutional Review Board/ethics committee approval was not required because this study was based on public records, as a systematic review and meta-analysis. The search strategy is displayed in Table 1 and a summary of the protocol is presented thereunder. This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocol.[12] The review protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews) (registration number: CRD42023252522) to enhance reliability.

Information sources

Two review authors (EG and AB) independently identified candidate studies through an electronic search of four databases: PubMed, Embase, Web of Science and Scopus. They used the following Medical Subject Heading terms: 'otologic brain complications' OR 'otologic brain abscess' OR 'otologic cerebral abscess' OR 'otologic brain infection' OR 'otologic cerebral infection' OR 'otologic brain suppuration' OR 'otologic cerebral suppuration' AND 'surgical treatment' OR 'surgical management' AND 'conservative treatment' OR 'conservative management' AND 'symptoms' OR 'bacteriology' OR 'morbidity' OR 'mortality' in any possible combination. There was no limitation in terms of publication date. The literature was last accessed in April 2023. Finally, the references of the resulting full texts were searched for further relevant citations.

Eligibility criteria

We primarily focused on randomised, controlled trials, and in their absence we looked for observational studies and case-series studies reporting on complications associated with otogenic brain complications. The review process was limited to English literature. In addition, we discarded editorials, reviews and meta-analyses, underpowered studies (fewer than five patients) and studies including exclusively paediatric populations.

Study selection

After duplicate removal, the two review authors (AB and KV) independently assessed the retrieved articles for title and abstract relevance. They then evaluated their full texts according to the predefined eligibility criteria. Disagreement between the reviewers was resolved through discussion with the senior author (JH). The remaining studies formed the basis of the systematic review and meta-analysis. The process of study selection is outlined in the flowchart shown in Figure 1.

Data collection

Each study was identified by the name of the first author and the year of publication. We collected the following data: (1) the type of study, (2) the size of the patient sample and its demographic characteristics, (3) technical details regarding the surgical procedure and (4) the number of patients presenting with complications, including deaths.

Quality appraisal in individual studies and overall evidence

Two other review authors (EG and AMN) performed the quality appraisal of the collected articles, independently, based on the type of the study. Risk of Bias In Non-randomised Studies of Interventions-I (ROBINS-I) and the (National Institute of Health) NIH Quality Assessment Tool were chosen for the quality appraisal of the non-randomised studies.[13,14] The ROBINS-I assessment tool evaluates every individual study apropos seven separate domains and each study was assumed to be of 'Low', 'Moderate', 'Serious' or 'Critical' risk of bias, depending on their evaluation score.[13] Accordingly, the NIH Assessment Tool, based on nine separate domains, assesses each study and defines it as 'Good', 'Fair' or 'Poor' quality.[14]

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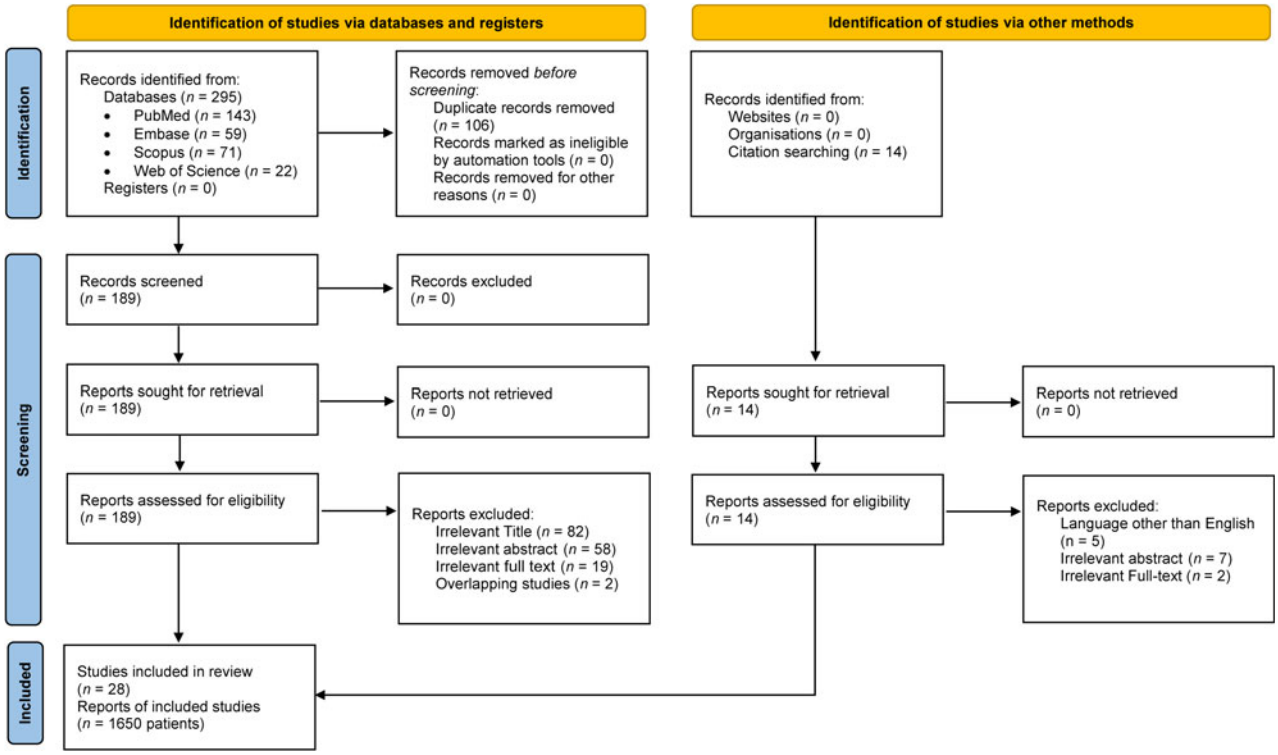

Figure 1. PRISMA Flowchart.

The quality of the overall body of evidence was assessed on each question, according to the Grading of Recommendations Assessment, Development and Evaluation working group as 'High' (Grade 4), 'Moderate' (Grade 3), 'Low' (Grade 2), or 'Very Low' (Grade 1).[15] In the case of disagreement, the authors reached a consensus after consulting the senior author (JH).

Data synthesis and statistical analysis

Fixed- and random-effects model meta-analysis was conducted to assess the proportion estimate for each outcome individually with more than three studies, while the inter-study heterogeneity was measured by the I^2 statistic. A value of I^2 less than 25 per cent was regarded as low heterogeneity, 25–75 per cent as moderate heterogeneity and greater than 75 per cent as severe heterogeneity. The results were visualised in forest plots. We estimated the risk for publication bias using Egger's regression test. Subgroup analysis was used to identify differences between the utilised techniques. In cases with extreme statistical heterogeneity, we re-ran the analysis after omitting the study with the greater contribution to the inter-study heterogeneity based on Baujat plots. We used the statistical environment R for all statistical analyses.[16] Significance was set at $p < 0.05$, and for complications associated with zero events we used a continuity correction equal to 0.5.

Results and analysis

Literature search

In total, 309 studies were identified by the literature search. Specifically, 295 were retrieved through databases, whereas 14 were obtained by searching the reference lists of the eligible full texts. Overall, 281 studies were excluded for reasons such as duplication irrelevance of the title, abstract or full text, and overlapping (Figure 1).

Eligible studies

Twenty-eight articles, written in the English language and published between 1972 and 2020, were considered eligible and were included in the qualitative and quantitative synthesis. All of the articles were non-randomised observational studies. The characteristics of the included studies are presented in Table 2.

Quality of evidence

According to the ROBINS-I risk of bias assessment tool, 6 of the included studies were evaluated as having a 'Moderate' risk of bias, 14 of them as having a 'Serious' risk of bias and 8 presented as having a 'Critical' risk of bias. Based on the NIH quality assessment tool 18 studies were rated as 'Good', 9 as 'Fair' and 1 as 'Poor'. Concerning the quality of the overall body of evidence, 98 different outcome arms were assessed. Mainly as a result of the presence of high risk of bias, imprecision and inconsistency matters, the evaluation resulted in 'Very Low' quality of evidence for each one of these arms (Supplementary Material Tables S1–S3).

Epidemiology

Overall, 1650 patients were encompassed in the systematic review. Among them 65 per cent (95 per cent confidence interval (CI): 60–70 per cent) were male and 35 per cent (95 per cent CI: 30–40 per cent) were female. Specific details regarding age were not provided by most of the studies. In those where relevant data were available, the patients' ages ranged from 4 months to 79 years. In 66 per cent of patients (95 per cent CI: 51–82 per cent) with an otogenic brain infection there was a known history of chronic otitis media, whereas acute otitis media was diagnosed in 33 per cent

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Table 2. Study characteristics

Studies	Study period	Number of patients	Males/ females	Brain complications	COM (cholesteatoma)	Mortality	Full recovery
Wolfowitz (1972)[17]	1968–1971	28	17/11	BA: 3, EDA: 8, SDA: 5, MEN: 26, VST: 12	26 (9)	9	19
Wright and Grimaldi (1973)[18]	1961–1978	36	NM	BA: 18, SDA: 2, MEN: 9, VST: 2	NM	2	NM
Lund (1978)[19]	1961–1977	50	NM	BA: 2, SDA: 2, MEN: 16, VST: 2	50 (47)	NM	NM
Bradley *et al.* (1984)[8]	1950–1979	127	99/40	BA: 115, EDA: 3, SDA: 4	124	60	23
Samuel *et al.* (1986)[20]	1978–1983	224	132/92	BA: 53, EDA: 49, MEN: 83, VST: 39	NM	32	NM
Kulali *et al.* (1990)[21]	1988–1989	14	8/6	BA: 4	4 (4)	3	7
Singh and Maharaj (1993)[22]	1985–1990	268	170/98	BA: 84, EDA: 21, SDA: 27, MEN: 22, VST: 36	268 (143)	15	NM
Kurien *et al.* (1998)[23]	1991–1996	36	27/9	BA: 26, SDA: 10, MEN: 18, VST:2	36 (36)	0	36
Djeric *et al.* (2003)[4]	1975–2000	42	NM	BA: 42, MEN: 25	35 (35)	8	34
Seven *et al.* (2004)[24]	1992–2002	11	6/5	BA: 2, EDA: 3, MEN: 4, VST: 11	11 (9)	0	8
Leskinen and Jero (2005)[25]	1990–2004	50	30/20	BA: 4, MEN: 4, VST: 1	6 (4)	5	NM
Özkaya *et al.* (2005)[5]	1993–2002	25	19/6	BA: 25	14 (11)	4	15
Penido *et al.* (2005)[26]	1987–2002	33	19/14	BA: 26, EDA: 2, SDA: 2, MEN: 26, VST: 5	27 (26)	3	22
Bento *et al.* (2006)[27]	2003–2010	24	18/6	BA: 8, EDA: 4, MEN: 7, VST: 5	17 (14)	0	24
Hafidh *et al.* (2006)[11]	1997–2004	12	10/2	BA: 5, VST: 4	8 (3)	0	NM
Morwani (2009)[28]	1985–2004	61	NM	BA: 18, 29, SDA: 2, MEN: 2	36 (25)	2	52
Alaani (2010)[29]	1998–2003	6	3/3	BA: 6, SDA: 2	1 (1)	0	6
Dubey (2010)[30]	1993–2007	32	21/11	BA: 10, EDA: 7, SDA: 2, MEN: 14, VST: 2	32 (31)	10	NM
Wanna (2010)[31]	1998–2007	10	8/2	BA: 5, SDA: 1, VST: 4	9 (3)	0	10
Nawaz (2013)[32]	2005–2010	42	29/13	BA: 10	42 (18)	0	NM
Borgohain (2015)[9]	2013–2014	17	12/4	BA: 17	10 (10)	0	NM
Sharma (2015)[10]	1999–2010	45	27/18	BA: 13, EDA: 2, SDA: 2, MEN: 6, VST: 5	NM	0	22
Mukherjee *et al.* (2016)[6]	2009–2014	22	17/5	BA: 22	22 (7)	2	14
Laulajainen-Hongisto *et al.* (2017)[33]	1970–2012	18	16/2	BA: 16, SDA: 1, MEN: 7	18 (14)	3	NM
Van der Poel *et al.* (2017)[2]	2008–2017	47	24/23	BA: 5, EDA: 8, SDA: 6, MEN: 19, VST: 22	6 (6)	10	NM
Burton *et al.* (2019)[3]	2008–1014	252	158/94	BA: 252, MEN: 66	NM	12	NM
Yakobi *et al.* (2019)[34]	2008–2015	77	49/28	BA: 36, EDA: 20, SDA: 22, VST: 15	47 (35)	13	NM
Song *et al.* (2020)[7]	2008–2019	41	27/14	BA: 41	41 (28)	7	NM

COM = chronic otitis media; BA = brain abscess; EDA = epidural abscess; SDA = subdural abscess; MEN = meningitis; VST = venous sinus thrombosis; NM = not mentioned

(95 per cent CI: 10–57 per cent) of the included patients. On clinical examination, a cholesteatoma was recognised in 53 per cent (95 per cent CI: 42–64 per cent) of cases and 17 per cent (95 per cent CI: 5–28 per cent) of patients had preciously undergone ear surgery. Six studies provided data regarding the general medical history: 9 per cent of patients (95 per cent CI: 1–16 per cent) had diabetes mellitus, 19 were positive for HIV and 6 were positive for mycobacterium tuberculosis (Table 3).

Microbiology

Our meta-analysis showed that 16 per cent (95 per cent CI: 5–28 per cent) of the infections were related to multiple pathogens. Among the single pathogens, *Proteus mirabilis* was identified in 13 per cent (95 per cent CI: 8–18 per cent) of infections, followed by *Pneumococcus* (7 per cent, 95 per cent CI: 2–12 per cent) and *Pseudomonas aeruginosa* (6 per cent, 95 per cent CI: 3–8 per cent) (Table 4).

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Table 3. Epidemiological results of the included studies

Parameter	*k*	Proportion	Model	I^2	Publication bias
Males	24	0.65 (0.60–0.70)	RE	72.5	0.544
Females	24	0.35 (0.30–0.40)	RE	72.97	0.511
Right ear	7	0.36 (0.20–0.53)	RE	87.0	<0.001
Left ear	7	0.39 (0.23–0.23)	RE	85.51	0.016
Bilateral ears	3	0.16 (0.07–0.25)	FE	33.8	0.543
AOM	8	0.33 (0.10–0.57)	RE	98.19	0.730
COM	18	0.66 (0.51–0.82)	RE	99.17	0.110
Cholesteatoma	23	0.53 (0.42–0.64)	RE	96.24	0.057
Previous ear surgery	6	0.17 (0.05–0.28)	RE	88.77	0.870
Diabetes	4	0.09 (0.01–0.16)	RE	83.66	0.476

k = number of studies; RE = random effects; FE = fixed effects; AOM = acute otitis media; COM = chronic otitis media; GT = granulomatous tissue

Clinical presentation

The most common symptoms that were detected throughout all studies were purulent otorrhoea (84 per cent, 95 per cent CI: 74–94 per cent), headache (65 per cent, 95 per cent CI: 50–79 per cent), otalgia (45 per cent, 95 per cent CI: 28–61 per cent), fever (44 per cent, 95 per cent CI: 29–59 per cent), vomiting or nausea (44 per cent, 95 per cent CI: 28–61 per cent) and nystagmus (44 per cent, 95 per cent CI: 15–73 per cent). Less commonly mentioned clinical manifestations were drowsiness and/or altered mental status, meningeal irritation, papilloedema, dysdiadochokinesia, mastoid process tenderness and balance disturbances (Table 5).

Imaging and otogenic brain infections

Imaging examinations completed the diagnostic process in most cases. Specifically, CT was used in 75 per cent of cases (95 per cent CI: 54–95 per cent, $I^2 = 99.39$) and MRI in 36 per cent of cases (95 per cent CI: 7–65 per cent, $I^2 = 99.64$). A brain abscess was diagnosed in 49 per cent of cases (95 per cent CI: 35–64 per cent). A brain abscess was located in the cerebellum in 23 per cent of patients (95 per cent CI: 13–33 per cent). Multiple intracranial abscesses were detected in 12 per cent of patients (95 per cent CI: 0–25 per cent). Other brain complications secondary to otogenic infections were meningitis (34 per cent, 95 per cent CI: 23–45 per cent), sinus thrombosis (22 per cent, 95 per cent CI: 11–34 per cent) and hydrocephalus (12 per cent, 95 per cent CI: 6–19 per cent). Intratemporal complications were also encountered (Table 6).

Management

Among the included studies, 24 provided information regarding treatment. A combination of surgical and conservative therapy was chosen in 84.3 per cent of cases, whereas according to 8 studies conservative treatment alone was used in 4.0

Table 4. Microbiological results

Parameter	*k*	Proportion	Model	I^2	Publication bias
No growth	14	0.40 (0.25–0.54)	RE	96.05	0.451
Single organism growth	7	0.44 (0.35–0.53)	RE	31.78	0.920
Multiple organisms growth	8	0.16 (0.05–0.28)	RE	92.48	0.017
Proteus mirabilis	14	0.13 (0.08–0.18)	RE	67.1	<0.001
Pneumococcus	4	0.07 (0.02–0.12)	FE	0.0	0.998
Pseudomonas aeruginosa	13	0.06 (0.03–0.08)	FE	7.8	<0.001
Streptococcus Group A	11	0.06 (0.02–0.10)	RE	57.94	<0.001
Proteus vulgaris	3	0.05 (0.01–0.09)	FE	0.0	0.439
Enterococcus	11	0.04 (0.02–0.07)	FE	7.86	0.077
Staphylococcus aureus	12	0.04 (0.01–0.06)	FE	0.12	0.003
Escherichia coli	13	0.03 (0.01–0.05)	FE	0.0	0.128
Streptococcus viridans	3	0.02 (0.01–0.06)	FE	0.0	0.669
Bacteroides	11	0.02 (0.01–0.04)	FE	0.0	0.062
Peptostreptococcus	11	0.02 (0.01–0.04)	FE	0.0	0.375
Fusobacterium	10	0.02 (0.00–0.04)	FE	0.0	0.295
Haemophilus	10	0.02 (0.00–0.04)	FE	0.0	0.321
Streptococcus Group F	9	0.02 (0.0–0.05)	FE	0.0	0.383
Klebsiella	11	0.02 (0.0–0.04)	FE	0.0	0.009

k = number of studies; RE = random effects; FE = fixed effects

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Table 5. Clinical presentation

Parameter	*k*	Proportion	Model	I^2	Publication bias
Otorrhoea	13	0.84 (0.74–0.94)	RE	96.38	<0.001
Headache	14	0.65 (0.50–0.79)	RE	94.89	0.016
Otalgia	9	0.45 (0.28–0.61)	RE	89.69	0.613
Fever	14	0.44 (0.29–0.59)	RE	97.11	0.744
Vomiting/nausea	13	0.44 (0.28–0.61)	RE	97.33	0.589
Nystagmus	6	0.44 (0.15–0.73)	RE	96.68	0.355
Drowsiness	4	0.41 (0.14–0.69)	RE	94.6	0.354
Papilloedema	10	0.39 (0.26–052)	RE	90.5	0.626
Neck stiffness	12	0.39 (0.21–0.57)	RE	98.38	0.669
Dysdiadochokinesia	5	0.38 (0.05–0.71)	RE	96.96	0.752
Mastoid tenderness	4	0.35 (0.08–0.78)	RE	98.86	0.716
Balance disturbances	6	0.32 (0.09–0.55)	RE	96.7	0.730
Meningism	5	0.30 (0.15–0.40)	RE	84.7	0.042
Consciousness disturbances	12	0.27 (0.14–0.40)	RE	94.98	0.160
Ataxia	8	0.25 (0.10–0.40)	RE	91.94	0.012
Irritability	8	0.22 (0.11–0.32)	RE	75.41	0.015
Post-auricular fistula	3	0.18 (0.08–0.28)	RE	50.7	0.052
Vertigo	9	0.17 (0.10–0.23)	RE	55.47	<0.001
Hemiplegia	3	0.14 0.07–0.22)	FE	0.0	0.483
Facial nerve palsy/ paralysis	13	0.14 (0.09–0.19)	RE	80.45	0.570
diplopia	4	0.11 (0.05–0.17)	FE	0.0	0.411
Hemiparesis	5	0.10 (0.03–0.17)	RE	68.07	<0.001
Epileptic seizure	11	0.09 (0.07–0.12)	FE	9.9	0.365
Aphasia	8	0.08 (0.03–0.12)	RE	42.0	<0.001
Opthalmoplegia	6	0.07 (0.01–0.14)	RE	52.7	0.005
Photophobia	3	0.05 (0.03–0.08)	FE	0.0	0.435

k = number of studies; RE = random effects; FE = fixed events

per cent. As far as surgical management is concerned, 43.2 per cent of patients underwent exclusively an otological operation, 11.0 per cent of the patients were operated on solely by neurosurgeons and 36.9 per cent received a combined otolaryngological and neurosurgical intervention (Table 7).

Recurrence and mortality

According to 27 studies the mortality rate due to otogenic brain infection was estimated to be as high as 11.1 per cent (95 per cent CI: 7.1–15.1 per cent, $I^2 = 90.78$). Based on 15 reports, 71.0 per cent (95 per cent CI: 55.0–86 per cent, $I^2 = 98.41$) of patients fully recovered. A recurrence of the brain infection after the initial treatment was observed in 10.0 per cent of cases (95 per cent CI: 4.0–16.0 per cent, $I^2 = 87.37$).

Discussion

Although otogenic brain complications constitute a rare entity nowadays, they still can be encountered, even in developed countries. Because of the special characteristics of this entity regarding its pathogenesis and treatment, only a limited number of large studies was detected in the international medical literature. Most relevant data are retrieved from case reports or case series, therefore the development of a standard aspect concerning its presenting symptoms, culpable pathogens, management and mortality rates is challenging.[35]

In our analysis we investigated the aforementioned parameters and managed to come to some noteworthy deductions. The most usual initial clinical presentation included purulent otorrhoea (84 per cent), headache (65 per cent), otalgia (45 per cent), and fever and nausea (44 per cent). In 33 per cent of cases, patients suffered from acute otitis media, with no past history of otological infections.

Computed tomography had a principal contribution in early diagnosis because it was used in 75 per cent of cases. Brain abscess was the most common complication detected (49 per cent). The combination of surgical and conservative treatment was chosen as more appropriate in 84.3 per cent of cases.

Regarding surgical management, 36.9 per cent of patients received a combined otological and neurosurgical intervention, whereas 43.2 per cent had an exclusively otological operation and 11.0 per cent of patients were operated on solely by neurosurgeons. Unfortunately, no correlation was detected between the mortality and/or morbidity rates and the type of surgical management because in most of the studies the final outcomes were presented as general results and not separated into subgroups in relation to the treatment that occurred.

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Table 6. Brain complications

Parameter	*k*	Proportion	Model	I^2	Publication bias
Brain abscess	23	0.49 (0.35–0.64)	RE	99.42	0.296
– Brain abscess with cholesteatoma	3	0.17 (0.04–0.29)	RE	86.32	0.409
– Brain abscess with acute otitis media	3	0.03 (0.01–0.06)	FE	0.0	0.386
Cerebral abscess	21	0.34 (0.24–0.45)	RE	96.5	0.02
Cerebellar abscess	19	0.23 (0.13–0.33)	RE	95.57	0.251
Perisinus abscess	6	0.12 (0.07–0.18)	RE	56.61	0.002
Epidural abscess	12	0.17 (0.09–0.24)	RE	93.36	0.006
Subdural abscess	15	0.08 (0.05–0.12)	RE	81.15	<0.001
Multiple intracranial abscesses	6	0.12 (0.0–0.25)	RE	95.66	0.100
Meningitis	17	0.34 (0.23–0.45)	RE	96.74	0.153
Venous sinus thrombosis	15	0.22 (0.11–0.34)	RE	97.2	0.049
– Venous sinus thrombosis with acute otitis media	3	0.07 (0.02–0.17)	RE	92.26	0.955
Hydrocephalus	8	0.12 (0.06–0.19)	RE	61.15	0.671
Intratemporal complications	9	0.48 (0.27–0.70)	RE	0.125	99.21
Mastoid abscess	4	0.37 (0.03–0.70)	RE	99.51	0.277
Acute mastoiditis	6	0.41 (0.15–0.67)	RE	99.2	0.008

k = number of studies; RE = random effects; FE = fixed events

As far as demographic factors are concerned, sex was the only one for which appropriate data were available to be analysed, resulting in a male predominance of 65 per cent. Because a quantitative analysis for age was not possible, a qualitative review of the available information concluded that otogenic brain complications were more frequent in paediatric populations. This fact is in line with the higher prevalence of mastoiditis in children, as indicated by the literature.[36,37] As a result, the immature immune system and the misprision of personal healthcare that characterises this age group develops susceptibility to otogenic complications.[38] In view of this, the current review excluded studies encompassing exclusively paediatric patients to minimise the risk of bias.

Race was investigated only in the study by Burton *et al.*, who found a 45-fold rise in mortality rates among Black patients in comparison with rates in White patients.[3] According to previous studies, Black populations have been associated with poorer outcomes in acute otitis media in paediatric populations, which has been ascribed to differences in healthcare access, diagnostic testing and subspecialty clinical examination.[39–41] Given that there is scarce relevant information regarding the adult population, there is a considerable need for evaluation of how racial and other socioeconomic disparities may render some populations more vulnerable to otogenic brain complications.

The most frequent clinical presentations among the eligible studies included otalgia (45 per cent), purulent otorrhoea (85 per cent) and headache (65 per cent). During the initial otolaryngological examination, these subtle symptoms could be considered normal findings of a middle-ear infection, without raising the suspicion of an intracranial complication.

As ascertained by our study, signs indicating neurological impairment, such as altered mental status, meningeal irritation, nerve palsies and vomiting, arise less commonly, mainly accompanying more advanced cases.[35] Furthermore, despite the general belief that otogenic brain complications occur almost always in patients with chronic otitis media with or without cholesteatoma, our results show that a noteworthy number of patients (33 per cent) suffered from acute otitis media. Hence, acute ear infections should not be underestimated and considered less risk-bearing in patients without any past history of otological infectious disease.

On the other hand, it is a matter of fact that any chronicity of middle-ear disease provides the opportunity for a treatment intervention before any brain complications develop because these patients are forced to be under medical surveillance as a result of their primary condition.[34] However, undoubtedly for every patient, with or without a pre-existing history of chronic ear disease, presenting with newly emerging symptoms of headache, fever and vomiting, a CT or MRI scan of the temporal bone and the brain should be considered as a necessary first-line diagnostic tool.[35]

As indicated by our results, otogenic infections may arise from various sources, such as pathogens of the respiratory system, gastrointestinal system and skin. In our review, a single bacterial pathogen was isolated in 44 per cent of cases, and *Proteus mirabilis* was the most commonly identified microorganism. As mentioned in the study by Duarte *et al.*, which found the same bacterium to be the main pathogen of brain abscesses of otogenic origin, this is a rather unexpected finding given that *Proteus* species are not one of the usual pathogens found in the middle ear.[35] This could be caused by the high percentage of chronic ear disease among the patients (66 per cent) because the bacteria responsible for acute otitis media are different from those of chronic otitis media.[42] Nevertheless, it cannot be ignored that microbiological results may be affected by the empiric antibiotic treatment that patients were possibly receiving at the time of culture collection.

As far as the management of otogenic brain infections is concerned, there are no standard guidelines in the current literature. A combination of surgical and systematic treatment

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Table 7. Management details

Studies	Surgical + antibiotics treatment					Antibiotics treatment alone
	Number of patients	Total	Neurosurgical intervention alone	ENT intervention alone	Combined ENT and neurosurgical intervention	
Wolfowitz (1972)[17]	28	28	0	25	3	0
Wright and Grimaldi (1973)[18]	36	34	12	10	11	2
Lund (1978)[19]	50	50	3	NM	NM	0
Bradley *et al.* (1984)[8]	127	NM	12	NM	10	2
Samuel *et al.* (1986)[20]	224	136	0	83	53	0
Kulali *et al.* (1990)[21]	14	13	10	2	1	1
Singh and Maharaj (1993)[22]	268	268	0	87	181	0
Kurien *et al.* (1998)[23]	36	36	0	0	36	0
Djeric *et al.* (2003)[4]	42	42	NM	NM	NM	0
Seven *et al.* (2004)[24]	11	11	0	9	2	0
Leskinen and Jero (2005)[25]	50	46	0	42	4	4
Ozkaya *et al.* (2005)[5]	25	25	0	0	25	0
Penido *et al.* (2005)[26]	33	26	NM	NM	NM	7
Bento *et al.* (2006)[27]	24	22	0	18	4	2
Hafidh *et al.* (2006)[11]	12	NM	NM	4	3	NM
Morwani and Jayashankar (2009)[28]	61	61	0	0	61	NM
Alaani *et al.* (2010)[29]	6	6	0	5	1	0
Dubey *et al.* (2010)[30]	32	31	NM	24	5	1
Wanna *et al.* (2010)[31]	10	10	0	9	1	0
Nawaz *et al.* (2013)[32]	42	42	NM	5	NM	0
Borgohain *et al.* (2015)[9]	17	17	NM	5	12	NM
Sharma *et al.* (2015)[10]	45	45	NM	20	NM	0
Mukherjee *et al.* (2016)[6]	22	22	0	0	22	0
Laulajainen-Hongisto *et al.* (2017)[33]	18	18	4	NM	1	0
Van der Poel *et al.* (2017)[2]	47	43	NM	29	NM	4
Burton *et al.* (2019)[3]	252	NM	21	115	32	NM
Yakobi *et al.* (2019)[34]	77	NM	NM	12	59	NM
Song *et al.* (2020)[7]	41	33	11	6	16	8

NM = not mentioned

with antibiotics for at least four weeks constitutes the consensus.[7] The surgical strategy consists of a combination of neurosurgical and otological approaches to allow both brain complications and the primary pathology to be eliminated, preferably in a one-stage surgical procedure.[6,7]

In our study, the available data were not strong enough to form statistically significant deductions. Hence, the provided information was only qualitatively reviewed. In most of the cases, surgical management accompanied by initiation of empirical intravenous antibiotics was preferred. Surgery options consisted mainly of mastoidectomy, followed by either burr hole drainage or craniotomy. As previously mentioned, the details obtained were insufficient to compare the different types of surgical procedures that were performed in terms of mortality or recurrence rates.

In an effort to investigate the importance of mastoidectomy in this kind of patient, Burton *et al.* concluded that even though mortality was higher when mastoidectomy was not performed, there was not a statistically significant difference between the two groups to support its use.[3] Subsequently, future studies attempting a subgroup analysis would be useful to detect any association between the type of surgical intervention and the final outcomes of patients with brain complications of otogenic origin.

Whereas specific antibiotics were usually not reported in the eligible studies, the general approach consisted of broad-spectrum antibiotics targeting the most common pathogens. When specified, the most frequently chosen antibiotics were penicillin, cephalosporines, metronidazole, aminoglycosides and chloramphenicol in different dosages and combinations.

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Solely conservative treatment, which according to Song *et al*. is probably connected to the highest mortality rate, was used only in cases where surgical treatment was not possible.[7]

Over the years, mortality rates of otogenic brain complications have been reduced as a result of great progress in the fields of antibiotics, imaging and surgical techniques, but this reduction depends on several factors.[17] Age is the most significant factor because the presence of co-morbidities as well as the preference for initial sole conservative management in adults in comparison with children worsens the prognosis.[3] Furthermore, the longer the interval between symptoms onset and treatment, the more severe the sequelae.[43] On the other hand, according to other studies encountered in the literature, a higher (Glascow Coma Scale) GCS score on admission day was connected to a poorer final result.[7,44]

This study is characterised by several weaknesses that might affect its ability to reach extensively applicable conclusions. First and foremost, the inclusion and exclusion criteria probably increased the risk of bias. Large studies that would potentially deserve to be reviewed may have been excluded because of age and language limitations. The nature of this medical condition restricts the possibility of randomised studies, hence only case series where data were retrospectively collected were encountered in the literature. Furthermore, the lack of a standardised way of managing of this disease, in terms of time of intervention and type of surgery, as well as differences in the presentation of the outcomes limited the information that was available for statistical analysis. The risk of bias was evaluated as moderate or higher, and the overall quality of results were estimated as very low, hence the potency of our outcomes was probably downgraded.

Conclusion

Nowadays, otogenic brain complications constitute a rare entity, especially in developed countries, yet they may arise as a sequela not only of chronic, but also acute ear disease. A high index of suspicion should be indicated by the treating physician when a combination of ear inflammation and a new onset of symptoms such as headache, fever, nausea and altered mental status emerges. An early imaging examination may set the final diagnosis and lead to a prompt treatment initiation, which usually consists of the administration of wide-spectrum antibiotics, followed by surgical intervention.

- Otogenic brain complications are rare but life-threatening conditions that require a high index of suspicion
- A fixed- and random-effects model meta-analysis was conducted to examine the presentation, treatment, bacteriology and mortality rates of otogenic brain complications
- The most usual otogenic brain complications are brain abscess (49 per cent), meningitis (34 per cent) and sinus thrombosis (22 per cent)
- Symptoms include otorrhoea (84 per cent), headache (65 per cent), otalgia (45 per cent), fever (44 per cent), vomiting/nausea (44 per cent) and nystagmus (44 per cent)
- Prompt imaging examination facilitate diagnosis and lead to effective treatment with a combination of surgical intervention and antibiotics, minimising the mortality and morbidity rates

Because of the absence of standard guidelines regarding surgical management, which depends on the type of intracranial complication and the treating physician's assessment of the case, otological or neurosurgical interventions may be performed, either solely or combined. However, given the nature of the disease and hence the high heterogeneity among the eligible studies, no statistically significant correlation between the type of surgical treatment and the final mortality and morbidity outcomes was possible through this meta-analysis. These aforementioned factors should be addressed appropriately in future studies, where a subgroup presentation and analysis of the patients' demographics and clinical data may allow the deduction of safely applicable conclusions.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0022215124000343

Competing interests. None declared

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