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Management of drop attacks in Ménière's disease: a systematic literature review

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Abstract

Objectives. Drop attacks are described as an instantaneous fall to the ground, occurring without warning and without loss of consciousness, a consequence of abrupt deformation of the otolithic membrane due to high endolymphatic pressure. Drop attacks present significant injury risk, therefore effective treatment is imperative. This review is the first to examine all evidence for the management of drop attacks in Ménière's disease, and make recommendations.

Methods. We conducted a systematic literature review. Inclusion criteria consisted of all published English language examining treatments of drop attacks in Ménière's disease.

Results. One hundred and five articles were identified, 19 met criteria (case series and/or cohort studies). Two articles identified conservative treatments, eight examined intratympanic gentamicin, seven examined surgery, one examined all three and one examined intratympanic dexamethasone.

Conclusion. Evidence for the management of drop attacks in Ménière's disease is limited due to small studies. Some surgical approaches have limited effect. Intratympanic dexamethasone remains a promising treatment; further research is recommended.

Review Article

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Introduction

Alex Tumarkin was the first to describe a drop attack of peripheral vestibular origin in 1936, eponymously named Tumarkin's otolithic crisis.[1] It was defined as an instantaneous fall to the ground that occurs without warning and without loss of consciousness. The etiology of drop attacks is presumed to be an abrupt mechanical deformation of the otolithic membrane due to high endolymphatic pressure and subsequent stimulation of the vestibulospinal reflex pathways through the saccule and/or utricle.[2] Drop attacks can be a feature of Ménière's disease or secondary endolymphatic hydrops (with an incidence of 7 per cent[3]) and often present at the end stage of disease.[1,2,4] There is heterogeneity in reports of onset, frequency and duration of drop attacks in patients suffering with Ménière's disease (secondary endolymphatic hydrops); some can have an isolated episode, others can have weekly attacks lasting years. Wu *et al.*[5] observed disease duration of Ménière's disease in patients suffering from drop attacks is longer than in those without. Additionally, magnetic resonance imaging studies found significantly greater degrees of endolymphatic hydrops in this group.

Drop attacks present significant risk of injuries because of their unpredictable nature, as such, effective treatment of these events is imperative. Papers have reported various treatment strategies from conservative measures to ablative surgical procedures. To date there has not been a summary of evidence for treatment strategies of drop attacks. We conducted a systematic review of the evidence and make recommendations to aid clinicians' management of this rare but disabling sequelae of endolymphatic hydrops.

Materials and methods

Literature search strategy

The review was conducted using the principles as recommended by Tawfik *et al.*[6] The PICO (population, intervention, comparison, outcome) tool was utilized to develop our literature search strategy.[7] A structured literature search was conducted across six individual bibliographic databases: Cochrane Library, PubMed, MEDLINE, Embase, Emcare, and CINAHL (cumulative index to nursing and allied health literature) using a combination of natural (textword) and controlled (subject headings) vocabulary for terms related to Meniere's disease AND drop attacks.

Table 1. Summary of papers examining conservative treatment strategies; DA = drop attack; ITG = intratympanic gentamicin; VNS = vestibular nerve section

Author	Year	Country	Study design	Sample size	DA defined	DA outcomes as subgroup analysis	Intervention	Findings
Baloh *et al.*	1990	USA	Case series	12	Yes	No	Salt restriction and vestibular sedatives	Spontanous remission of DAs with persistance of vertigo (short follow-up period)
Janzen *et al.*	1988	Canada	Case series	6	Yes	No	Observation post initial treatment failure (vestibular sedatives, 2 had endolymphatic shunts)	Spontaneous resolution within 6 months of onset, with 4-year follow up
Lelonge *et al.*	2021	France	Case series	7	Yes	No	Oral betahistine (48 mg/day) plus acetyleucine (2 g/day) with salt modifications	No further DAs (follow up 1–19 years). Destructive techniques (ITG/VNS) offered for severity of vertigo and high-risk outcomes of DAs (7/15).

Table 2. Summary of papers examining intratympanic steroids; DA = drop attack; ITD = intratympanic dexamethasone; ITG = intratympanic gentamicin

Author	Year	Country	Study design	Sample size	DA defined	DA outcomes as subgroup analysis	Intervention	Findings
Liu *et al*	2016	China	Case series	7	Yes	No	Stacked dosing ITD (once a week for 4 weeks, repeated at 6 months if required)	5/7 no further DAs after one ITD, 1 no further DAs after 2 ITD, 1 no further after 2 ITD and 2 ITG.

Inclusion criteria

Inclusion criteria consisted of all published literature available in English examining treatment strategies for the management of drop attacks (including subgroup analysis). All study types were eligible, including conference publications.

Data extraction

The data extraction process of the included articles was carried out by the authors. Extracted data included year, country, study design, sample size, drop attack definition inclusion, treatment regime, follow-up period, and findings (including subgroup analysis findings). The extracted data were then compared and summarized in tables (Tables 1–4).

Drop attack definition criteria

Our definition of a drop attack includes the following criteria: (1) occurs in patients with definite Ménière's disease or endolymphatic hydrops; (2) a sudden fall that occurs without warning; (3) no associated loss of consciousness; (4) other causes for falls (e.g. cardiac, neurological, musculoskeletal) eliminated; or (5) drop attacks labelled as Tumarkin's otolithic crises.

Results

Literature search results

The results of the literature search are shown in Figure 1.

Conservative treatment for the management of drop attacks

Three studies were identified examining the use of more conservative treatment strategies or simply observation. Baloh *et al.*[2] examined the use of salt restriction and as required vestibular sedatives in 12 patients. The number of drop attacks (2–18) occurred with an interval of 62 days to 1 year. They described the majority of drop attacks spontaneously remitting after a one-year period (83 per cent) but with persistence of vertigo symptoms.[2] It is noteworthy that the time since the last attack was less than one year for 5 out of 12 patients.

Lelonge *et al.*[8] examined the use of high dose betahistine and acetylleucine (vestibular sedative) in seven patients. All patients had favourable outcomes, remaining drop attack free with a follow up of 1–10 years. It is important to mention that more severe cases in this study were managed with destructive treatments (intratympanic gentamicin/vestibular nerve section).

Janzen *et al.*[9] observed six cases of drop attacks and noted all experienced spontaneous resolution within six months, with no recurrence up to four years follow up. All the cases observed suffered with an initial cluster of attacks ranging from one to five, occurring over a period of one week to six months.

Intratympanic steroids for the management of drop attacks

One case series that was identified examining the effect of intratympanic dexamethasone on drop attacks met our drop attack definition criteria.[10] Seven patients were managed with intratympanic dexamethasone administered once a week for a total of four weeks, reviewed at six months and repeated if not controlled. These patients had failed an initial minimum six-month trial of lifestyle modifications, betahistine, diuretics and

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Table 3. Summary of papers examining intratympanic gentamicin; DA = drop attack; Gent = gentamicin; inj = injection(s); ITD = intratympanic dexamethasone; ITG = intratympanic gentamicin; MD = Ménière's disease; sx = symptoms; TDS = Three times daily

Author	Year	Country	Study design	Sample size	DA defined	DA outcomes as subgroup analysis	Intervention	Findings
Guan *et al*.	2022	China	Retrospective Cohort	81	No	Yes	ITG (1 ml of 40 mg/ml), repeat after 1/12 if failed, then stacked treatment (2/7 days)	Non subgroup analysis; DAs persisting after ITG 46/81 (56.7%), 41.2% success (62.4% 1 injection, 27.9% 2 inj, 9.7% 3–7 inj), 11.4% failure, 47.4% relapse (31.4% in 1 year, 31.4% 1–2 years, 37.2 >2 years)
Dallan *et al*.	2005	Italy	Case report	1	Yes	No	Tympanostomy tube 1ml of 26.7 mg/ml Gent TDS every 3 days for 35-day period. Continued until no further vertigo/ DAs occurred.	No further DA/vertigo (10 months post treatment)
Thomsen *et al*.	2000	Denmark	Case series	6	Yes	Yes	Intratympanic micro-catheter to RW, delivery of Gent at either 1 μl/hr or 10 μl/hr (mean of 5.6 or 41 mg Gent /mean 40 days.	4/6 no longer had DA
Viana *et al*.	2014	USA	Case series	23	Yes	No	1 m of 40 mg/ml ITG injection, repeat at 1/12 if no resolution, if >3/12 post first then consider a new cycle	20/24 DA controlled after 1 ITG cycle, 23/24 after 2–4 ITG cycles
Wu *et al*.	2019	China	Prospective Cohort	16	Yes	Yes	1 x ITG (1.5 ml of 30 mg/ml) no. of DA measured/month for 6 months prior to and after ITG	14/16 no further DA. 11/13 complete control vertigo, 1/13 class B, 1/13 class c.
Lelonge *et al*.	2021	France	Prospective Cohort	7	Yes	No	ITG 0.5 ml of 40 mg/ml (2–10 injections, one month interval)	No further DAs at 3 years+ post ITG
Liu *et al*.	2017	USA	Case series	13	Yes	Yes	ITG 1 ml 40 mg/ml titrated (2, 1 month apart then 2, 3–4 days apart until sx improved) if failed offered labyrinthectomy.	83% complete control DA in MD+ migraine and 100% in MD without migraine. ($P > 0.999$)
Murofushi *et al*.	1997	Australia	Case series	6	Yes	Yes	ITG 0.5–1 ml 30 mg/ml given 2–5 injections on consecutive days (if signs /sx of inner ear destruction then stopped). Second set given of 2–5 injections. Total activity in the caloric tests measured at 1–2 months post injections.	3 no further DA/vertigo, 3 persistent vertigo, 2 salvage labyrinthectomy
Odkvist *et al*.	1988	Sweden	Case series	28	Yes	Yes	ITG 0.5–1 ml of 40 mg/ml buffered with 25% Sodiumbicarb given daily until destruction type nystagmus seen. 3–11 doses given.	No further DAs, 18/29 vertigo abolished, 9 occasional attacks, 2 recurrent attacks

vasodilators. Five patients (71 per cent) had complete resolution of drop attacks after one round of intratympanic dexamethasone, one patient (14 per cent) was satisfied after two rounds, and one patient required intratympanic gentamicin after two rounds of intratympanic dexamethasone failed. Follow-up periods were 19–34 months. No significant side effects were recorded; none showed conspicuous hearing loss, otitis media or tympanic membrane perforations during the follow-up period.

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Table 4. Summary of papers examining surgical strategies; DA = drop attack; VNS = vestibular nerve section

Author	Year	Country	Study design	Sample size	DA defined	DA outcomes as subgroup analysis	Intervention	Findings
Black *et al.*	1982	USA	Case series	9	Yes	No	6 ablative (3 labyrinthectomy, 3 vestibular nerve section), 3 shunt procedures (endolymphatic sac decompression) (2 converted to VNS)	No futher DAs after definitive intervention.
Kinney *et al.*	1995	USA	Case series	3	No	Yes	3 shunt procedures (cochleosacculotomy)	No further DAs, one patient's vertigo returned after one year.
McCall *et al.*	2007	USA	Case series	8	Yes	No	8 transmastoid labyrinthectomy	No further DAs
Bergmark *et al.*	2020	USA	Case series	43	No	Yes	43 transmastoid labyrinthectomy	No further DAs, 3 had persistent vertigo
Ishiyama *et al.*	2001	USA	Case series	7	Yes	No	2 vestibular nerve sections, 5 transmastoid labyrinthectomies	No further DAs, 5 had persistent vertigo
Montandon *et al.*	1988	Swizerland	Case series	2	No	Yes	2 ventilation tubes	DAs persisted
Véleine *et al.*	2022	France	Case series	18	Yes	Yes	18 retrosigmoid vestibular nerve sections	No further DAs, 10% had persistent vertigo
Lelonge *et al.*	2021	France	Case report	1	Yes	No	1 vestibular nerve section	No further DAs

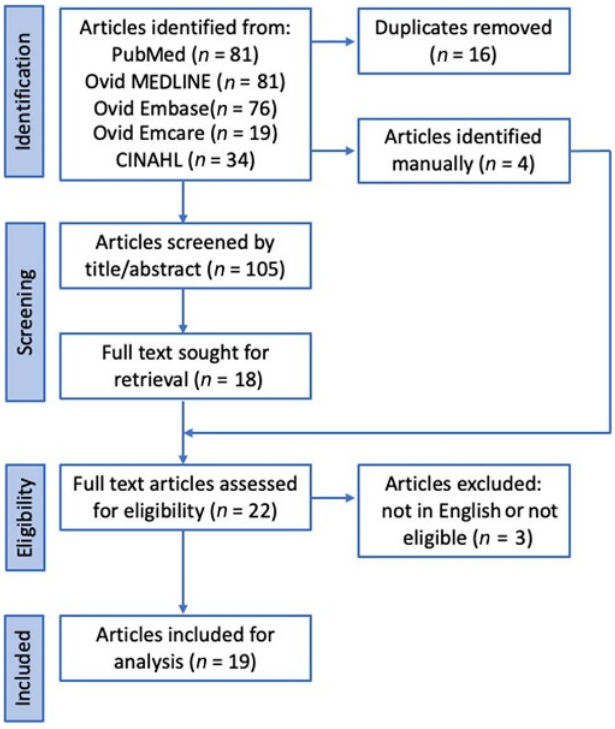

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analyses ('PRISMA') flowchart showing the article selection process for this review.

Intratympanic gentamicin for the management of drop attacks

Nine papers were identified examining the effect of intratympanic gentamicin on drop attacks. Six were case series, two were prospective cohort studies, and one was a retrospective cohort study. Eight papers met our drop attack definition criteria. Drop attack outcomes were part of subgroup analysis in six papers. Pre-treatment management of patients was discussed in six papers, all of which failed lifestyle modifications and medical therapy. A combined total of 181 patients received intratympanic gentamicin for treatment of drop attacks.

Intratympanic gentamicin regimes varied. The most common dosing regime was 0.5–1 ml of 40 mg/ml gentamicin delivered with trans-tympanic injection in staggered doses until the desired effect was achieved (five papers with a combined total of 160 patients).[7,11–14] Two papers used a lower dose of 0.5–1.5 ml of 30 mg/ml gentamicin with trans-tympanic injection, one[15] gave a one-off dose (1.5 ml) (16 patients) and the other[16] gave daily doses (0.5–1 ml) until the effect was achieved (six patients).

Two papers trialled novel delivery approaches. One[17] used a tympanostomy tube for infiltration of 1 ml of 26.7 mg/ml gentamicin three times per day every three days for a period of 35 days (one patient). The other[18] inserted an intratympanic microcatheter situated next to the round window and delivered an infusion of gentamicin, totalling either 5.6 mg or 41 mg, over a period of 40 days (six patients).

Post-treatment drop attack outcomes for patients given staggered doses of 1 ml of 40 mg/ml gentamicin were 43–100 per cent success rate (no further attacks). The study with the largest population[11] demonstrated the poorest outcomes; 43 per cent of 81 patients no longer suffered with drop attacks at six-month follow up. Odkvist *et al.*[13] and Lelonge *et al.*[7] found all their patients were cured from drop attacks (28 patients with 1–9 year follow up and 7 patients with 1–19 year follow up, respectively). Viana *et al.*[14] found 83 per cent (20/24) of patients were cured from drop attacks after one cycle and 96 per cent (23/24) after two cycles of intratympanic gentamicin injections. Liu *et al.*[12] found a greater rate of drop attack resolution when treating patients without migraine (100 per cent *vs* 83 per cent).

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Eighty-eight per cent of 16 patients receiving 1.5 ml of 30 mg/ml gentamicin had no further drop attacks (six months to two years post treatment).[15] Murofushi *et al.*[16] found 50 per cent of six patients receiving staggered doses of 0.5–1.5 ml of 30 mg/ml gentamicin were cured at one-year follow-up.

The microcatheter delivery system[17] showed a 67 per cent resolution (4/6) of drop attacks at 9–12 months and the tympanostomy tube technique completely resolved drop attacks for the individual case in which it was used.[18]

Side effects experienced by patients receiving staggered doses of 1 ml of 40 mg/ml gentamicin include vestibular and audiological. Guan *et al.*[11] reported 10.2 per cent suffered with persistent disequilibrium along with 54 per cent of Liu *et al.*'s patients.[12] In terms of audiological side effects: Guan *et al.*[11] report an average increase in pure tone audiometry thresholds by 18.6 dB and a decrease in word discrimination by 33 per cent; Viana *et al.*[14] reported that pure tone average thresholds increased by >10 dB in 47 per cent of patients; and Odkvist *et al.*[13] reported 14.3 per cent of patients developed post-treatment dead ear, an overall average of 6 dB threshold increase on pure tone average, and a mean speech discrimination drop by 5 per cent.

Wu *et al.*[15] reported no significant hearing loss post treatment with an individual dose of 1.5 ml 30 mg/ml intratympanic gentamicin. Murofushi *et al.*[16] (staggered doses of 0.5–1 ml of 30 mg/ml intratympanic gentamicin) reported 94 per cent of patients developed acute vestibular symptoms and 28 per cent continued to have chronic symptoms. Thomsen *et al.*[18] (microcatheter delivery system to the round window) noted 22.2 per cent of patients developed anacusis of the treated ear, whilst with the tympanostomy tube delivery system[17] noted their patient developed a transient disequilibrium that resolved with vestibular rehabilitation.

Surgical treatment for the management of drop attacks

Eight papers examined surgical interventions for the management of drop attacks. All studies were retrospective case series or case reports. Drop attack outcomes were part of subgroup analysis in four papers. Five papers met our drop attack definition criteria.

Pre-treatment management of patients was not discussed in four papers. Black *et al.*[19] trialled patients on oral or intravenous vestibular suppressants prior to surgical management. Eighty-six per cent of all patients in the Bergmark *et al.*[20] study had prior treatment with intratympanic gentamicin. Montandon *et al.*[21] trialled all patients on anti-vertiginous medication. Véleine *et al.*'s patients[22] received prior medical treatment: 21 per cent had non-specified surgical treatment and 13 per cent had chemical labyrinthectomy (intratympanic gentamicin).

Surgical approaches for the treatment of drop attacks can be subdivided into shunt or ablative procedures. Six patients across two studies received shunt procedures (three had endolymphatic sac decompression),[19] and three had cochleosacculotomy.[23] Of the three patients who had endolymphatic sac decompression, one had no further drop attacks but persistent vertigo and two had persisting drop attacks (overall 33 per cent success rate). No specific complications were discussed for these patients undergoing shunt procedures, however two patients proceeded with vestibular nerve sections, and one had a revision cochleosacculotomy.

Eighty-three patients across six studies underwent ablative procedures; 59 patients had transmastoid labyrinthectomies, 24 patients underwent vestibular nerve sections. All patients post transmastoid labyrinthectomies or vestibular nerve section procedures were free from drop attacks. Two studies examining ablative procedure outcomes did not comment on complications.[7,24]

In regards to vestibular nerve sections, complications included transient facial nerve palsy (2.7 per cent and 40 per cent for Véleine *et al.*[22] and Black *et al.*,[19] respectively), complete hearing loss (20 per cent for Black *et al.*[19]) and increased pure tone average thresholds (15.6 per cent for Véleine *et al.*[22]). Other complications included diplopia (9.5 per cent), cerebrospinal fluid leak (6.8 per cent), cicatricial (9.5 per cent), bilateral pulmonary emboli (2.7 per cent) and incomplete section (2.7 per cent).[22]

Bergmark *et al.*[20] reported the following transmastoid labyrinthectomies complications: wound infection (2.5 per cent), transient facial nerve palsy (2.5 per cent), return to the emergency department for side effects related to post-operative medication (4.2 per cent), cerebrospinal fluid leak (1.4 per cent) and the need for mastoid obliteration (1.4 per cent). There was a report of a stroke by McCall *et al.*[25] (12.5 per cent). Montadon *et al.*[21] examined the use of transtympanic ventilation tubes, but no effect was observed.

Analysis

Drop attacks are an infrequently encountered symptom of a rare pathological process. NICE quotes the incidence rate for Ménière's disease in the UK to be 13.1 per 100,000[26] and the pooled incidence of criteria-meeting-drop attacks in Ménière's disease is 7 per cent.[3] The rarity of this phenomenon results in small population study groups, making opportunities to conduct high quality research difficult. Our systematic literature review identified that current evidence consists mainly of case studies or reports with only a few prospective and/or retrospective cohorts. Therefore this body of evidence currently lacks statistical significance. Furthermore some studies included in this review examined drop attacks and treatment outcomes as a subgroup analysis,[11–13,15,16,20–23] which reduces the power of the results as the risk of false positives and negatives increases.[27]

Our literature review highlights four main treatment approaches to the management of drop attacks: conservative approaches with use of lifestyle and medication (such as vestibular sedatives and betahistine), intratympanic steroids, intratympanic gentamicin, and surgery (shunt or ablative procedures).

Conservative treatment for the management of drop attacks

The papers examining conservative approaches have significant heterogeneity and examine drop attack patients at varying stages and severities of disease. Broadly, the patients managed with diet, lifestyle and medication alone had lower symptom severity or had acquiescent periods after an initial cluster of attacks. The follow-up period for a proportion of these patients was also relatively short, which limits reliability. The field of novel conservative treatment options remains promising: an in-vitro mouse model investigating the effect of spironolactone (aldosterone antagonist) on endolymphatic hydrops identified several molecular pathways in which spironolactone inhibits endolymphatic hydrops progression, and some which do not. Furthermore immunostaining identified aldosterone target receptors in the apical part of the human saccule, indicating its translational potential for human use. The results indicate a personalized medical approach may need to be taken in the future, depending on which molecular mechanism induces endolymphatic hydrops in the individual.[28]

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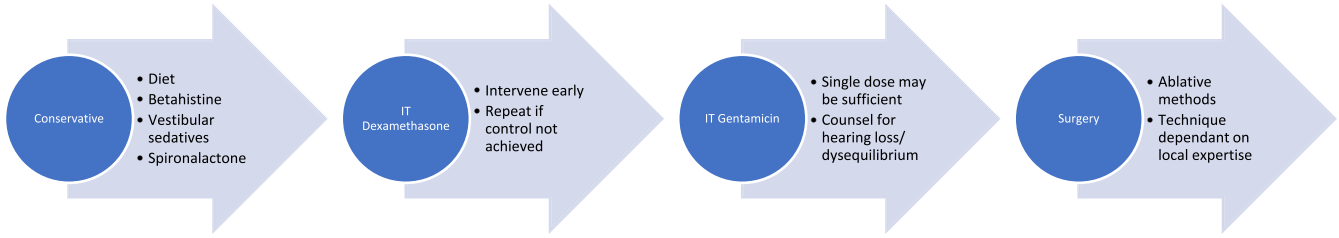

Figure 2. Treatment escalation strategy for management of drop attacks

Intratympanic steroids for the management of drop attacks

One paper[10] examined the use of intratympanic dexamethasone where previous maximal medical therapy had failed. The sample size was small (7), but the results seem promising with 6/7 not requiring further destructive techniques. This technique also had very low associated morbidity which gives it significant advantage over intratympanic gentamicin methods. Evidence for the effectiveness of intratympanic dexamethasone can be sought from a double-blinded randomized controlled trial investigating the use of intratympanic steroids for the management of Ménière's disease where 82 per cent of patients achieved complete vertigo control with dexamethasone compared to 57 per cent with placebo.[29]

Intratympanic gentamicin for the management of drop attacks

Intratympanic gentamicin has the largest body of evidence with the predominant indication being prior failure to manage symptoms with diet, lifestyle and maximal medical therapy. There was significant variation of dosing and frequency of treatment regimes. Due to heterogeneity it is not possible to collate results, however, broadly speaking, this method appears to be effective for the management of drop attacks with a success range of 43–100 per cent.

Limitations of this method include requirement for multiple courses and therefore hospital visits and side effects such as persistent disequilibrium and increased pure tone average thresholds. Two double-blinded randomized controlled trials[30,31] investigating the use of intratympanic gentamicin for management of Ménière's disease found an average increase of 18.1dB HL, which is comparable to our literature search findings. An additional limitation to consider is the possibility of salvage labyrinthectomy where there is treatment failure with intratympanic gentamicin; two such patients underwent this in Murofushi's study.[16]

Surgical treatment for the management of drop attacks

Surgical management of drop attacks has the second largest body of evidence with eight papers identified. Broadly, two surgical strategies are employed: shunt procedures such as endolymphatic sac decompression and/or cochleosacculotomy, and ablative procedures such as transmastoid labyrinthectomy and vestibular nerve sections. Overall, only six patients identified in the literature were managed with shunt procedures and details of previous treatment strategies for these patients were not discussed. Additionally there is a high conversion or revision rate, with half requiring further procedures. There is 100% drop attack resolution following ablative procedures, however there is significant associated morbidity with this procedure.

Discussion

This publication represents the first literature review examining all the current evidence for the management of drop attacks in Ménière's disease. The body of evidence is currently limited to case studies and series or cohort studies of small sample sizes. The conclusions that can be drawn from the limited data available support a treatment escalation strategy (Figure 2), starting with interventions with the lowest associated morbidity. We recommend an initial trial of optimized maximal medical therapy (diet, betahistine, infrequent use of vestibular sedatives and consider a trial of spironolactone) with close clinical review. If drop attacks persist, we recommend early intervention with intratympanic dexamethasone, to be repeated if symptom control is not achieved. Failing this, ablative interventions should be considered starting with a trial of intratympanic gentamicin (noting a single injection may be sufficient), whilst limiting the chances of hearing loss. Repeated dosing and time intervals should be based upon local experience and services. Patients should be counselled for hearing loss and disequilibrium risks. We also recommend salvage treatment with ablative surgery if intratympanic gentamicin fails and drop attacks remain troublesome, and once patients have been fully counselled of the risks. The operative technique should depend on local expertise.

We recommend further large-scale studies to be conducted to improve the reliability of the interventions discussed, particularly studies examining the effect of intratympanic dexamethasone on drop attacks.

- Drop attacks are a rare phenomenon of Ménière's disease (7 per cent occurrence)
- There is no current consensus on the management of drop attacks
- We identified a stepwise approach to managing drop attacks through conducting a systematic literature review
- Management of drop attacks mirrors the stepwise management recommendations for traditional Ménière's disease
- Use of intratympanic dexamethasone is a particularly promising strategy, however little research currently exists for its use in drop attacks

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