Systemic aminoglycosides-induced vestibulotoxicity in humans

Systemic aminoglycosides-induced vestibulotoxicity in humans: a systematic review

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ABSTRACT

Objectives: This systematic review aimed to investigate the prevalence and characteristics of vestibular adverse effects of aminoglycoside (AG) therapy in humans and to analyse objective vestibular tests for the detection of AG-induced vestibulotoxicity. **Design:** PubMed, Cochrane Database, Web of Science, and reference lists of all included studies were screened by two independent researchers. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed. Studies were included according to pre-set inclusion criteria and reported outcomes of studies evaluating vestibular function using one or more objective vestibular function tests in adults and/or children after systemic AG administration. The methodological quality of each study was assessed using the Quality Assessment Tool for Quantitative Studies. Interrater reliability was established using Cohen's Kappa. **Results:** Twenty-seven studies were included, with the vast majority showing AG-induced vestibulotoxic side effects, ranging from 0% to 60%. Most studies reported AG-induced abnormalities by caloric and rotatory testing, whereas only a few studies reported using video Head Impulse Test (vHIT) and Vestibular Evoked Myogenic Potential (VEMP) testing. **Conclusion:** Since type I hair cells (particularly of the semicircular canals) are more susceptible to ototoxicity, vHIT and VEMP testing seem more promising for the early detection of vestibulotoxicity than caloric and rotatory testing. Prospective studies using an extensive vestibular test battery are needed to further characterize the impact of AGs on the different vestibular end organs and to identify the most sensitive vestibular technique for the early detection of vestibulotoxicity.

Keywords: Aminoglycosides, systematic review, vestibular, vestibular screening, ototoxicity, vestibulotoxicity.

INTRODUCTION

Aminoglycosides (AG) are broad-spectrum antibiotics that are commonly prescribed in life-threatening diseases, such as multidrug-resistant tuberculosis, sepsis and cystic fibrosis, due to their antimicrobial efficiency, widespread availability and cost-effectiveness (Caminero et al. 2010; Gibson et al. 2003; Pillers et al. 2005; Schatz et al. 2005). Since the use of streptomycin, the first discovered AG, it became clear that AGs may induce nephro- and ototoxicity (Hinshaw et al. 1947). Despite the recognized risk for these side effects, AGs are still frequently administered (Grohskopf et al. 2005; Hermann 2007; Price 1986). The overall reported incidence of AG-induced ototoxicity varies from 2%-25% (Esterhai et al. 1986; Fee 1980; Rizzi et al. 2007). Based on histological studies, AGs induce sensory hair cell injury. Prolonged exposure of inner ear cells to AGs is associated with destruction of outer hair cells (OHC) in the organ of Corti and type I vestibular hair cells in both the crista ampullaris and maculae, leading to auditory and vestibular impairment (Carey et al. 2002; Chiodo et al. 1994; Forge et al. 2000; Huizing et al. 1987; Lyford-Pike et al. 2007). The pathogenesis of AG-induced hair cell injury remains elusive. Several hypotheses have been reported (Forge and Schacht 2000; Poirrier et al. 2010; Rizzi and Hirose 2007; Selimoglu 2007) with oxidative stress considered to be the principal mechanism. Literature suggests that cellular injury depends on AG binding with iron to form a toxic metabolite, which generates hydroxyl radicals that place the cell under oxidative stress (Poirrier et al. 2010; Rizzi and Hirose 2007; Selimoglu 2007), resulting in apoptotic cell death. Although all AGs may damage both cochlear and vestibular structures, individual AGs differ in their propensity to produce cochleo- or vestibulotoxicity. Neomycin, kanamycin and amikacin are more cochleotoxic, whereas vestibular damage is generally triggered by gentamicin and streptomycin (Matz 1993; Rybak et al. 2007; Selimoglu et al. 2003).

The clinical features of AG-induced cochleotoxicity are frequently discussed (Chen et al. 2013; Farzal et al. 2016; Prayle et al. 2010; Rybak and Ramkumar 2007; Schacht et al. 2012). Since OHCs at the cochlear base are more susceptible to toxicity than apical hair cells, high frequencies are generally more severely affected (Fausti et al. 1984) resulting in a high-frequency sensorineural hearing loss, often accompanied by tinnitus. With continued exposure, hair cell damage progresses to the apex, placing patients at increased risk for further hearing impairment (Huizing and de Groot 1987). Distortion product otoacoustic emissions and high-frequency audiometry are internationally recommended as the most sensitive tests for cochleotoxicity (Al-Malky et al. 2015; Farzal et al. 2016; Geyer et al. 2015; Stavroulaki et al. 1999; Tange et al. 1985).

Vestibulotoxicity from systemic AGs in humans is less frequently described, which may be due to the presenting symptoms of vestibulotoxicity. Both ears are often affected, resulting in oscillopsia, chronic disequilibrium and postural instability (Black et al. 1993; Lucieer et al. 2016; van de Berg et al. 2015; Ward et al. 2013), symptoms which are often underappreciated by clinicians as relating to the ear, compared to tinnitus or spinning vertigo. These symptoms of vestibulotoxicity are often attributed to the underlying diseases, for which AGs were prescribed, and are often discovered late because patients receiving AG therapy are often bedridden. Finally, vestibular organ failure may be masked by sensory substitution by vision and proprioception, obscuring vestibular damage compared to the more salient effects of cochlear damage (van de Berg et al. 2015).

Cochlear and/or vestibular dysfunctions can influence academic performance, social, cognitive and mental development (Davis et al. 1986; van de Berg et al. 2015), which may result in a diminished quality of life (Guinand et al. 2012; Mendel et al. 1999; Stevenson et al. 2015; Sun et al. 2014). Therefore, routine screening for audiovestibular side effects should be

conducted during (and after) AG therapy, such that AG administration can be stopped or adjusted in time to prevent ototoxic damage (Ariano et al. 2008; Black et al. 2001; Leis et al. 2015). In contrast to the monitoring of cochleotoxic effects, there is no standardized protocol to screen for AG-induced vestibulotoxicity.

The aim of this systematic review is to determine the prevalence and characteristics of vestibular adverse effects of AG therapy in humans and to analyse objective vestibular techniques for early detection of systemic AG-induced vestibulotoxicity.

METHODS

This study was performed according to the international Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Liberati et al. 2009).

Search strategy

A systematic literature search was conducted using PubMed, Web of Science and Cochrane databases. The search strategy was based on keywords derived from the PICOS approach (Participants, Intervention, Comparison, Outcome and Study design). The articles had to report outcomes of vestibular function evaluation using one or more objective vestibular function tests (O) in adults and/or children (P) (before and) after systemic AG administration (I). Because of the limited amount of data on vestibulotoxicity, all types of group designs (C and S) were accepted. The keywords used for the literature search are represented in Table 1.

Study selection

Based on the selection criteria (Table 2), the title and abstract of all retrieved articles were screened, followed by a full-text screening of the selected articles. If the study did not meet the selection criteria, the article was excluded. An additional 'hand search' was conducted by screening the reference lists of all included studies, to prevent missing useful citations. The

literature search and screening procedure was conducted by two independent researchers, with calculation of Cohen's Kappa score (Landis et al. 1977) to determine the level of interrater agreement. The cut-off date for articles to be included was November 2016.

Data extraction

The following items were collected from each included study: author and year, study design, patient information (sample size, sex ratio, mean age and pathology/infection for which AGs were prescribed), information about control group, information about AG use (applied AG, dose, duration and manner of administration), additional cochlear toxicity, objective vestibular function tests (choice of test and time of evaluation), vestibular outcome measures, main findings on vestibular symptoms and tests, as well as recommendations for screening.

Risk of bias assessment and level of evidence

The methodological quality of all included articles was evaluated using The Quality Assessment Tool For Quantitative Studies (developed by the Effective Public Health Practice Project (EPHPP)) (Thomas et al. 2004), which rates six methodological study parameters: selection bias, study design, potential confounding variables (predetermined before bias assessment was started), blinding, data collection methods and withdrawals and dropouts. The overall study quality was considered to be 'strong' if none of the parameters was rated as 'weak', 'moderate' if one parameter was rated as 'weak', and 'weak' if two or more parameters were rated as 'weak' (EPHPP 2009a, 2009b). The overall methodological quality score was not used as criterion for eligibility because of the limited existing literature on this topic. However, bias assessment was conducted to enhance the consistency of the results and to reveal further information about flaws in the literature. Additionally, the level of evidence was determined for each article and its study design based on the Oxford Centre for Evidence-based Medicine-Levels of Evidence guidelines (Phillips et al. 2009).

RESULTS

A total of 1361 records were retrieved from the electronic databases (Pubmed: 658; Cochrane Database: 38; Web of Science: 665). A summary of the search results and reasons for exclusion are depicted in Figure 1. The percentage of interrater agreement between the two investigators was high (95.9%), yielding a very good interrater agreement kappa score of 0.814 (SE = 0.039) (Landis and Koch 1977).

Characteristics of the included studies

The 27 studies consisted of randomized controlled trials (n=2), a controlled clinical trial (n=1), prospective cohort studies (n=12), cross-sectional studies (n=9) and retrospective case series (n=3), all of which are represented in Table 3. The publication year ranged from 1973 (Elfving et al. 1973; Tjernstrom et al. 1973) to 2016 (Ahmed et al. 2016). The sample size of the study participants varied from 10 (Gendeh et al. 1993) to 418 (Kim et al. 2011). The 27 relevant articles comprised a total of 1675 patients treated with AGs. The mean age ranged from 2.4 days (Finitzo-Hieber et al. 1979) to 70.0 years (Ahmed et al. 2011). A detailed description of the study characteristics is represented in Table 3.

Risk of bias assessment and level of evidence

As measured by the EPHPP tool (Thomas et al. 2004), two (7%) studies were rated as strong (Fee 1980; Lerner et al. 1986), ten (37%) as moderate (Ahmed et al. 2011; Barza et al. 1980; Black et al. 2004; Finitzo-Hieber et al. 1979; Gendeh et al. 1993; Gendeh et al. 1991; Kim et al. 2011; Lehmann et al. 1976; Pedersen et al. 1987; Zagólski 2008) and fifteen (56%) as weak (Agrawal et al. 2013; Ahmed et al. 2016; Aust 2001; Chen et al. 2013; Deka et al. 1977; Elfving et al. 1973; Eviatar et al. 1981; Hauch et al. 1986; Ishiyama et al. 2006; Noone et al. 1974; Scheenstra et al. 2009; Tjernstrom et al. 1973; Tjernstrom et al. 1982; Weber et al. 2009;

Winkel et al. 1978). Ratings for each individual parameter of the tool are represented in Table 4.

Thirteen of the fifteen studies that rated weak were mainly due to the lack of appropriate consideration of predetermined potential confounders (i.e. age, gender, renal insufficiency, pre-existing audiovestibular dysfunction, duration of AG therapy, total daily dose, previous AG exposure and co-administration of other agents). The second significant reason for the weak rating was study design and this was evident in ten of the fifteen studies; cross-sectional studies and case series were automatically considered as weak. Studies with a high dropout rate were assigned as weak. Most studies were rated as strong for data collection methods, because they used validated and reliable vestibular function tests. Nine of the twenty-seven studies (32%) were labelled as moderate for this parameter, since the judgement of the test results was based on visual evaluation (i.e. Frenzel goggles) by a single investigator. In only two studies (Fee 1980; Lerner et al. 1986) the researchers were not aware of the administered AG. Uncertainty of blinding was rated as moderate. Finally, the criteria for selection bias were mostly rated as moderate or weak because detailed information about the selection procedure was lacking.

Synthesis of the included studies

Characteristics of AG-induced vestibulotoxicity

In twenty-one studies, the prevalence of AG-induced vestibulotoxicity was identified. In the other six studies (Agrawal et al. 2013; Ahmed et al. 2011; Black et al. 2004; Deka et al. 1977; Ishiyama et al. 2006; Weber et al. 2009), the aim was to determine vestibular outcome measures in patients that were selected based on their known AG-induced vestibulotoxicity. As presented in Table 3, different types of AGs were used. The prevalence of vestibulotoxicity categorised by the type of AG is represented in Table 5.

The patients (in the prevalence studies) with reported vestibulotoxicity after AG-therapy (n=117) usually showed bilateral vestibular dysfunction (n=46), although in six studies unilateral dysfunction (n=11) was observed as well (Chen et al. 2013; Eviatar and Eviatar 1981; Noone et al. 1974; Scheenstra et al. 2009; Tjernstrom et al. 1982; Winkel et al. 1978). As reported in Table 3, in fourteen studies (52%), patients were questioned concerning vestibular symptoms after AG administration (Ahmed et al. 2011; Barza et al. 1980; Black et al. 2004; Deka et al. 1977; Fee 1980; Gendeh et al. 1991; Ishiyama et al. 2006; Kim et al. 2011; Lehmann et al. 1976; Lerner et al. 1986; Noone et al. 1974; Pedersen et al. 1987; Scheenstra et al. 2009; Tjernstrom et al. 1973). In these studies—except for two (Kim et al. 2011; Lerner et al. 1986)—vertigo, dizziness, disequilibrium and oscillopsia were the most reported symptoms (Black et al. 2004; Deka et al. 1977; Fee 1980; Ishiyama et al. 2006; Lehmann et al. 1976; Tjernstrom et al. 1973). In two studies (Black et al. 2004; Deka et al. 1977) nausea, headache, cognitive impairment and visual sensitivity were reported as well. However, lack of awareness of the vestibular impairment was also a frequent finding in other cases (Fee 1980; Lerner et al. 1986; Noone et al. 1974; Pedersen et al. 1987; Scheenstra et al. 2009; Tjernstrom et al. 1973).

Vestibulotoxicity was accompanied by cochleotoxicity in nine (Barza et al. 1980; Black et al. 2004; Deka et al. 1977; Elfving et al. 1973; Eviatar and Eviatar 1981; Fee 1980; Lerner et al. 1986; Tjernstrom et al. 1982; Winkel et al. 1978) of twenty studies (45%) in which the occurrence of cochleotoxicity was examined as well (Ahmed et al. 2011; Barza et al. 1980; Black et al. 2004; Chen et al. 2013; Deka et al. 1977; Elfving et al. 1973; Eviatar and Eviatar 1981; Fee 1980; Finitzo-Hieber et al. 1979; Gendeh et al. 1993; Gendeh et al. 1991; Kim et al. 2011; Lehmann et al. 1976; Lerner et al. 1986; Noone et al. 1974; Pedersen et al. 1987; Scheenstra et al. 2009; Tjernstrom et al. 1982; Winkel et al. 1978; Zagólski 2008). In one of the studies (Pedersen et al. 1987), patients showed AG-induced hearing loss, but it was unclear

whether these patients were the same as those in whom vestibulotoxicity was observed. In the remaining ten studies vestibulotoxicity occurred without accompanying cochlear damage. Deka, et al. (1977) and Kim, et al. (2011) noted that vestibulotoxic symptoms occurred earlier than cochleotoxic symptoms.

The vestibular test battery

An overview of the tests used in the included studies is reported in Table 3. In twenty-one studies (78%), the caloric test was the preferred vestibular function test for detecting vestibulotoxicity, and was the only vestibular test used in twelve studies (Barza et al. 1980; Deka et al. 1977; Fee 1980; Gendeh et al. 1993; Gendeh et al. 1991; Hauch et al. 1986; Lehmann et al. 1976; Lerner et al. 1986; Noone et al. 1974; Pedersen et al. 1987; Scheenstra et al. 2009; Tjernstrom et al. 1973; Tjernstrom et al. 1982; Winkel et al. 1978). In the twenty-one prevalence studies, the frequency of abnormal caloric responses post-AG ranged from 0% to 60%. In four descriptive studies (Agrawal et al. 2013; Ahmed et al. 2011; Black et al. 2004; Deka et al. 1977), an abnormal caloric response was observed in 75.5% - 100% of the cases. In these studies, however, the diagnoses were based on the absence of caloric-induced nystagmus. Reduction in the peak slow phase velocity (SPV) was the most commonly used criterion for the evaluation of vestibulotoxicity. For example Fee (1980) and Lerner, et al. (1986) used 33% and 50% respectively as the minimal reduction of the peak SPV. In the studies by Agrawal, et al. (2013), Eviatar and Eviatar (1981) and Scheenstra, et al. (2009) the responses were classified as abnormal if the peak SPV did not reach more than 5°/s, 10°/s or the values did not meet the predetermined norms. In a few studies, the SPV could not be calculated since the judgement of the vestibular response was based on qualitative evaluation (Ahmed et al. 2016; Barza et al. 1980; Gendeh et al. 1991; Hauch et al. 1986; Tjernstrom et al. 1982; Zagólski

2008). In the study of Pedersen et al. (1987) a reduction of at least 25% in the caloric sum was used.

Rotatory chair testing was the second most commonly used test of vestibulotoxicity and was also used in eight studies, while in four it was the only vestibular test used (Aust 2001; Elfving et al. 1973; Finitzo-Hieber et al. 1979; Gendeh et al. 1991). Three studies investigated the prevalence of vestibulotoxicity in children using the rotatory chair test. The prevalence of abnormal responses ranged from 0% (Aust 2001) to 100% (Ishiyama et al. 2006). In three descriptive studies (Black et al. 2004; Ishiyama et al. 2006; Kim et al. 2011) the rotatory chair parameters were described in detail. Black et al. (2004) found abnormal responses in all 33 subjects who were tested with single-sine and pseudorandom rotation stimuli. In eight study participants a normal VOR gain was found, whereas the time constant (T_c) was abnormal. In 23 subjects, both gain and T_c were significantly reduced. In the study of Ishiyama, et al. (1992) a reduced gain and increased phase were seen over the entire tested frequency range. However, the decrease in VOR gain was greater in the lower frequencies (0.05 – 0.2 Hz), whereas some patients had preserved gain at intermediate frequencies (0.8 Hz). Additionally, minimal responses to high acceleration step changes in velocity and a bilateral ultra-low VOR T_c could be observed. Kim, et al. (2011) observed abnormal VOR responses in 2.9% of their study participants. In comparison with the control group, VOR gain values were significantly lower at all three frequencies tested. Moreover, VOR gain values were significantly decreased at higher frequencies (0.04 - 0.16Hz) compared to the lower frequency (0.01Hz).

The horizontal head impulse test (Halmagyi et al. 1988) was used in five studies in patients with known AG-induced vestibulotoxicity (Agrawal et al. 2013; Ahmed et al. 2016; Ahmed et al. 2011; Ishiyama et al. 2006; Weber et al. 2009). In these studies, except for one (Weber et al. 2009), the detection of the catch-up saccades was based on clinical assessment and all

patients showed catch-up saccades during head impulses to one or both sides. In the study using search coils (Weber et al. 2009), bilateral symmetrical reductions of the VOR gain, depending on the degree of vestibulotoxicity, were seen in patients with known gentamicin-induced vestibulotoxicity. Additionally, the overt catch-up saccades were 5.6 times larger than in normal subjects.

For the evaluation of otolith organ function, oVEMP and cVEMP (Colebatch et al. 1992; Rosengren et al. 2005) were used in only one (Agrawal et al. 2013) and three studies, respectively (Agrawal et al. 2013; Chen et al. 2013; Zagólski 2008). All studies using cVEMP used 500 Hz tone burst to evoke a response, whereas the one study that used oVEMP used a mini-shaker to generate the response. In the study of Agrawal, et al. (2013), the study participants had bilateral vestibulopathy (BV) with different aetiologies, including nine with BV secondary to AG therapy. Sixty-four and 61% of all patients had a reduction of oVEMP and cVEMP amplitude respectively in comparison with the control group. Although not specifically discussed, the greatest reduction of VEMP amplitude was detected in patients with AG-induced BV. However, the difference in decreased amplitude was only significant in oVEMP testing. In the study of Chen, et al. (2013) three patients (13%) treated with amikacin had abnormal cVEMP amplitudes. Zagólski (2008) reported a similar prevalence of absent cVEMP responses (14%).

In the context of this review, other non-objective tests used were not described in detail.

As shown in Table 3, only 8/27 (30%) studies using a complementary test battery of these multiple objective tests (Agrawal et al. 2013; Ahmed et al. 2016; Ahmed et al. 2011; Black et al. 2004; Chen et al. 2013; Eviatar and Eviatar 1981; Ishiyama et al. 2006; Zagolski 2008). Three studies (Ahmed et al. 2016; Black et al. 2004; Eviatar and Eviatar 1981) discussed both caloric and rotatory test results. The clinical HIT as well as caloric test results were represented in the

studies of Agrawal et al. (2013), Ahmed et al. (2011) and Ahmed et al. (2016). Two studies estimated the outcome on both HIT and rotatory chair testing (Ahmed et al. 2016; Ishiyama et al. 2006). Lastly, the studies of Chen et al. (2013) and Zagólski (2008) discussed both the prevalence of abnormal caloric test results as well as abnormal cVEMP results. The prevalence of abnormal test results categorized by each study is shown in Table 6.

DISCUSSION

Vestibulotoxicity in humans

The considerable range (0%-60%) in prevalence of vestibulotoxicity is caused by many factors contributing to the amount and severity of AG-induced ototoxic side effects, including the type of AG, which may be more or less vestibulo- or cochleotoxic (Matz 1993; Rybak and Ramkumar 2007; Selimoglu et al. 2003). A systematic review conducted by Kahlmeter and Dahlager (1984), reported that among all AG adverse effects in clinical studies between 1975 and 1982, the highest prevalence of vestibulotoxicity was found in patients who were treated with amikacin, tobramycin and gentamicin. The results in the current systematic review support these findings, however streptomycin was found to be another important contributor to AG vestibulotoxicity (Table 5). Although there are many studies about vestibulotoxicity of diverse AGs, studies comparing side effects among different AGs are rare (Selimoglu et al. 2003). Consequently, whether a particular AG is more or less vestibulotoxic in humans is unknown.

Factors contributing to the amount of cochleotoxicity include pre-existing renal failure, cumulative exposure, duration of AG administration, co-administration of known ototoxic drugs, and increased age. (Forge and Schacht 2000; Govaerts et al. 1990; Rogers et al. 2011). Unfortunately, evidence to support the influence of these risk factors on vestibulotoxicity is

scarce (Ariano et al. 2008; Rogers and Petersen 2011). For example, there is some evidence that vestibulotoxicity due to systemic AGs is dose-dependent (Chen et al. 2013) but this finding needs to be corroborated. Although discussion of this information falls outside the scope of the study's objective, dosing data is consequently represented in Table 3. However, if these factors also contribute to the prevalence of vestibulotoxicity, the reported prevalence should be critically evaluated in studies that did not control for these confounding variables (Table 4). For example, the high upper level (60%) of the overall prevalence range was established by a study including only 10 patients with chronic renal failure in whom vestibular function tests were performed after cumulative exposure to gentamicin (Gendeh et al. 1993). On the other hand, in three studies, evidence of vestibulotoxicity was lacking, which may be explained by the use of a very low gentamicin dose (Gendeh et al. 1991), a low follow-up rate and the use of only one vestibular function test (Aust 2001; Hauch et al. 1986). Additionally, vestibulotoxicity was potentially under- or overestimated in other studies due to the similar flaws. Perhaps more important is the influence of baseline testing, which was lacking in twelve of the twenty-one prevalence studies and most likely resulted in an overestimation of vestibulotoxicity (Ahmed et al. 2016; Aust 2001; Chen et al. 2013; Elfving et al. 1973; Eviatar and Eviatar 1981; Finitzo-Hieber et al. 1979; Hauch et al. 1986; Kim et al. 2011; Noone et al. 1974; Scheenstra et al. 2009; Tjernstrom et al. 1973; Zagólski 2008).

The prevalence of AG-induced vestibular impairment in children is ambiguous as well. Three studies demonstrated a similar prevalence as in adults (Chen et al. 2013; Eviatar and Eviatar 1981; Zagólski 2008). In contrast, four studies found little or no signs of vestibulotoxicity (Aust 2001; Elfving et al. 1973; Finitzo-Hieber et al. 1979). Therefore, Aust (2001) suggested that children, and especially neonates, are less sensitive to AG adverse effects. However, it has to be noted that most of these studies performed examinations several years after the AG-

therapy (Eviatar and Eviatar 1981) and evaluation of the vestibular function was often based on clinical exam or the use of a single vestibular test.

Vestibular symptoms are possibly the earliest ototoxic effects of systemic AG therapy (Deka et al. 1977; Kim et al. 2011). However, the symptoms of vestibulotoxicity are usually unrecognized and inadequately reported (Halmagyi et al. 1994; Liu et al. 2015). This may be attributed to the bilateral nature of toxicity-induced vestibular deficits, resulting in rather vague symptoms, as reported in the current review (Ahmed et al. 2011; Black et al. 2004; Black and Pesznecker 1993; Deka et al. 1977; Ishiyama et al. 2006; Lucieer et al. 2016; van de Berg et al. 2015). Additionally, the patient may relate these symptoms to the underlying (often life-threatening) disease for which the AG treatment is given. Moreover, most of these patients are bedridden and symptoms will not be noticed until they start walking (Ahmed et al. 2012), resulting in a delayed onset of symptoms (Ahmed et al. 2011; Deka et al. 1977; Kim et al. 2011). In conclusion, since symptoms of AG-related vestibulotoxicity are rather vague, clinicians should specifically inquire about multiple vestibular symptoms (not only vertigo) after AG administration, as vestibular symptoms can have a considerable impact on someone's quality of life (Guinand et al. 2012; Mendel et al. 1999; Sun et al. 2014; van de Berg et al. 2015; Zingler et al. 2009).

As reported by several included studies, a significant amount of patients did not experience co-existing hearing impairment, suggesting that vestibulotoxicity can occur without accompanying cochleotoxicity (Ahmed et al. 2011; Chen et al. 2013; Finitzo-Hieber et al. 1979; Gendeh et al. 1993; Gendeh et al. 1991; Kim et al. 2011; Lehmann et al. 1976; Noone et al. 1974; Scheenstra et al. 2009; Zagólski 2008). Therefore, it is also important to screen for cochleo- and vestibulotoxicity separately (Ahmed et al. 2012; Dobie et al. 2006; Liu et al. 2015).

The vestibular test battery

Histologic examinations demonstrate that AGs can affect the whole vestibular sensorineural epithelium, with type I hair cells considered most susceptible components (Black and Pesznecker 1993; Lindeman 1969; Nakashima et al. 2000; Rybak and Ramkumar 2007; Tsuji et al. 2000; Zingler et al. 2009). Additionally, several histological and animal studies reported that the SCCs are more vulnerable to toxicity than the otolith organs (Ishiyama et al. 2007; Lindeman 1969; Nakashima et al. 2000; Sun et al. 2015; Tsuji et al. 2000).

For the detection of vestibulotoxicity, the majority of the included studies used caloric and rotatory chair testing, tests capable of examining the low and mid frequency range of the horizontal canal function, respectively (Goncalves et al. 2008; Maes et al. 2011; van de Berg et al. 2015; Wuyts et al. 2007). For caloric testing, the most important indication for vestibulotoxicity is a reduction in the SPV of the caloric-induced nystagmus (Agrawal et al. 2013; Ahmed et al. 2011; Barza et al. 1980; Chen et al. 2013; Eviatar and Eviatar 1981; Gendeh et al. 1993; Gendeh et al. 1991; Lerner et al. 1986; Pedersen et al. 1987; Tjernstrom et al. 1973). In the study of Pedersen, et al. (1987) the summated SPV was used as a criterion. Several studies concerning bilateral vestibular impairment endorse the use of caloric sum and suggest a limit of 20°/s to establish the diagnosis of bilateral vestibular dysfunction of the horizontal SCC (Hain et al. 2013; van de Berg et al. 2015). For rotatory chair testing, a reduction in VOR gain and reduced time constant (T_c) or increased phase are the most reported findings. To screen for bilateral vestibulopathy, some suggest using changes of the VOR T_c (or phase), rather than gain, which is influenced by the level of alertness of the patient (Li et al. 1991; Maes et al. 2008; van de Berg et al. 2015).

Over the last few years, new vestibular testing techniques have emerged, such as the video HIT and VEMP which provide complementary information to caloric and rotatory testing, since

VEMP techniques examine the otolith function (both saccule and utricle) and the video HIT provides additional high frequency information for each semicircular canal. Therefore, clinicians are now able to evaluate the function of all five different vestibular components. The HIT especially serves high frequency characterization of the horizontal, posterior and anterior SCC and seems to activate irregular afferents, which tend to innervate type I hair cells (Goldberg 2000; McCaslin et al. 2014; Wuyts 2008). To date, only five studies use the HIT (four used the clinical, subjective, HIT and one the video HIT) for the detection of AG-induced vestibulotoxicity, all showing a positive HIT on one (Ahmed et al. 2011) or both sides (Agrawal et al. 2013; Ahmed et al. 2016; Ahmed et al. 2011; Ishiyama et al. 2006; Weber et al. 2009). Only one study (Weber et al. 2009) assessed quantitative vHIT , reporting larger amplitudes of catch-up saccades than in normal subjects and a bilateral symmetrical reductions of VOR gain. Since the major affinity of AGs for type I SCC hair cell dysfunction is well-known, vHIT seems promising and requires further research with implementation of high-speed video goggles and evaluation of the vertical SCCs as well. Cervical and ocular VEMPs can examine the integrity of type I saccular and utricular hair cells, respectively (Agrawal et al. 2013; Curthoys et al. 2014; Lue et al. 2009), and were so far only used in three vestibulotoxicity studies (Agrawal et al. 2013; Chen et al. 2013; Zagólski 2008). As can be seen in the results, these three studies found a loss of the saccular function, with a similar prevalence for children treated with AGs (Chen et al. 2013; Zagólski 2008). Since the study of Agrawal et al. (2013) compared different etiologies of bilateral vestibulopathy, the authors did not report the prevalence of saccular or utricular dysfunction of patients with AG-induced vestibulotoxicity separately. However, due to the comparison of the different etiologies, the study showed that oVEMP results should be implemented in the screening for AG-induced. oVEMP amplitudes were significantly lower in patients with vestibulotoxicity due to AGs, which means that measurement of the utricular

function is important for the differential diagnosis of patients with bilateral vestibulopathy. For cVEMP, a reduction of both latency and peak-to-peak amplitudes was reported, whereas a reduction of the N1 oVEMP amplitude was seen in the study of Agrawal, et al. (2013). Since both the raw oVEMP amplitude (N1) and peak-to-peak cVEMP amplitude have shown to provide the most reliable information, both parameters can be used for the detection of vestibulotoxicity (Venhovens et al. 2015).

A study that assesses function of each vestibular end organ would be particularly clinically relevant. As can be seen in the results (Table 6), few studies assess multiple vestibular end organs. However, based on this data, some preliminary suggestions for screening can be made. Supported by studies using both caloric and rotation tests, AG administration appears to cause similar damage to both low and mid frequency function of the HSCC (Ahmed et al. 2016; Black et al. 2004; Eviatar and Eviatar 1981). This is in contrast to the high frequency horizontal canal function, which seems to be more affected after AG administration in the studies of Agrawal et al. (2013) and Ahmed et al. (2011). It should be noted however that the study subjects of Agrawal et al. (2013) and Ahmed et al. (2011) were selected, based on abnormal HIT and/or caloric responses. In these studies, therefore, all vestibulotoxic patients had both absent caloric responses in combination with bi- or unilateral positive HIT results. In the prospective study of Ahmed et al. (2016), positive clinical HIT responses were seen in 53% (17/32) of the patients, whereas 31% had pathological caloric and rotation outcomes after administration of streptomycin. Additionally, in the study of Ishiyama et al. (2006) the authors established that all patients had a positive bilateral HIT, whereas a few patients did have preserved gain results at intermediate frequencies and low accelerations by rotational testing while no response to high acceleration step changes could be observed. These findings are in agreement with the findings of histopathological studies demonstrating that type I hair cells

(high frequency detection) of the SCC are more vulnerable to AGs toxicity than other vestibular structures (Black and Pesznecker 1993; Lindeman 1969; Nakashima et al. 2000; Rybak and Ramkumar 2007; Tsuji et al. 2000; Zingler et al. 2009).

Two studies using caloric testing, also represented the prevalence of abnormal otolith function by using the cVEMP technique, which revealed conflicting data (Chen et al. 2013; Zagólski 2008). One study suggested that AG therapy causes damage to both SCC and otolith function, but function of the former structure is more frequently impaired. The other study discussed that 13% of the patients had abnormal VEMP responses, while only 4% of the patients suffered from SCC dysfunction (Chen et al. 2013). These latter findings can be supported by current histological studies, which suggest that type I hair cells (VEMP) are more affected in case of vestibulotoxicity. However, studies using VEMP techniques are too limited or different to compare and to draw any definite conclusion. The study of Agrawal et al. (2013) estimated the cVEMP and oVEMP results as well, although no prevalence data could be compared since the authors did not represent the test results of patients with vestibulotoxicity separately from the overall group of patients with bilateral vestibulopathy.

Based on these studies (and histological findings) and since vHIT and VEMP techniques tend to measure the type I hair cell function, both these tests seem promising for the detection of AG-induced vestibulotoxicity, in addition to caloric and rotatory testing (Black et al. 2004; Fee 1980; Ishiyama et al. 2006; Petersen et al. 2013; Weber et al. 2009; Zagólski 2008).

To confirm the diagnosis of vestibulotoxicity, these objective vestibular tests can be extended with other tests, such as the dynamic visual acuity and vestibulospinal reflex tests (e.g. Romberg test) (Demer et al. 1994; Fujimoto et al. 2009), which are frequently recommended to establish the diagnosis of bilateral vestibular impairment (Ahmed et al. 2011; Fujimoto et

al. 2009; Minor 1998; van de Berg et al. 2015). Additionally and of crucial importance is the performance of a thorough history taking.

The authors recommend to perform vestibular examination before, during and after AG administration for adequate screening and close follow-up in patients receiving AGs (Black et al. 2001; Ishiyama et al. 2006; Minor 1998; Tjernstrom et al. 1973; Tjernstrom et al. 1982). Baseline testing is necessary to detect subtle or exclude pre-existing vestibular dysfunction (Black et al. 2004; Fee 1980; Lehmann et al. 1976). Since literature suggests that early detection of vestibulotoxicity and cessation of the AG administration (if possible) can prevent further deterioration of the vestibular system (Ariano et al. 2008; Black et al. 2004; Ishiyama et al. 2006; Kim et al. 2011; Leis et al. 2015; Scheenstra et al. 2009), the vestibular assessment should be performed weekly if possible, during therapy (Ahmed et al. 2011; Fee 1980; Minor 1998). In some cases vestibulotoxicity effects as well as vestibular function recovery can occur after cessation of the AG therapy (Black et al. 2001; Black et al. 2004; Deka et al. 1977; Fee 1980; Kim et al. 2011; Lehmann et al. 1976; Winkel et al. 1978), follow-up testing should be performed for at least six months to one year after AG therapy (Black et al. 2001; Black et al. 2004; Vasquez et al. 2003).

Limitations and recommendations for further research

To date, there are several flaws in the published literature about vestibulotoxicity in humans. The current review shows that the existing evidence is insufficient to estimate the prevalence of AG vestibulotoxicity in adults and children, to identify the most vestibulotoxic AG type and to figure out whether the known risk factors for ototoxicity also apply to vestibulotoxicity. Furthermore, based on the present literature it is impossible to determine the part of the vestibular system that is most sensitive for AGs, since the current evidence is mainly based on evaluation of the horizontal SCC. Moreover, data comparing rotation or vHIT results with

VEMP outcomes are lacking and studies using a complete vestibular test battery in the same study subject(s) have not been performed.

The current systematic review also has several limitations. Firstly, a meta-analysis could not be performed because of the large heterogeneity in study methodologies. Secondly, a significant portion of the included studies had a low methodological quality. Nevertheless, studies at high risk for bias were included as well, to provide additional information for the current review. Finally, since non-English articles were excluded, language bias may have occurred.

In conclusion, the data presented in this review encourages close vestibulocochlear follow-up of patients before, during and after AG treatment and demonstrates the importance of developing specific screening protocols. As to which test would be the most appropriate for the early detection of vestibulotoxicity, no definite conclusion can be drawn as a large variation as well as conflicting results have been reported and the current evidence is mainly based on evaluation of the horizontal SCC alone. However, as stated earlier, in accordance with animal and histopathological studies, the current literature suggests that type I hair cells of the semicircular canals are most vulnerable to toxicity. vHIT and VEMP testing therefore seem the most promising for the detection of AG-induced vestibulotoxicity, in addition to caloric and rotatory chair testing. Moreover, these tests are short, easy to perform and can be performed in children, all of which are convenient advantages for patients who are bedridden or too ill for studies requiring more equipment such as caloric and rotatory chair testing. Additionally, the findings of this systematic review clearly emphasize the need for future high-quality prospective longitudinal studies including all above complementary objective vestibular tests and taking into consideration the discussed possible confounding factors, as pre-existing renal failure, cumulative exposure, duration of AG administration, co-

administration of known ototoxic drugs, increased age and possible genetic susceptibility, in order to compare the sensitivity of the vHIT and VEMP techniques for the early detection of vestibulotoxicity to the caloric and rotatory test.

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FIGURE LEGEND

Figure 1. Flowchart presenting a summary of the search results and the reasons for exclusion.