Chapter 11

Aldosterone assessment in patients
with Menière’s disease

Introduction

Since 1938 endolymphatic hydrops has been generally accepted as the basic histopathological substrate of Menière’s disease [1,2]. Hydrops is the consequence of a disturbance of the homeostasis of inner ear fluid. Hydrops can be caused by a reduced absorption and/or overproduction of endolymph [3,4].

In patients with Menière’s disease the size of the endolymphatic sac seems to be reduced, suggesting a reduction in resorptive capacity. Post-mortem histological investigations have revealed a significantly smaller vestibular aqueduct in patients suffering from Menière's disease [5,6]. In a recent three-dimensional magnetic resonance imaging (3DFT-CISS-MRI) study it was found that the size of the endolymphatic sac seemed to be significantly smaller in the ears of patients with Menière's disease as compared to those in the control group [7,8]. Differences observed between uni- and bilaterally affected patients (distance unilateral affection<bilateral affection<non-Menière) indicate that uni- and bilateral affection are two different entities [8,9]. This suggests that the size of the endolymphatic sac is not the only factor in the pathogenesis of Menière's disease. In unilaterally affected patients limited resorption, associated with the reduced dimensions of the endolymphatic sac, may play a major role in developing endolymphatic hydrops, whereas in bilaterally affected patients the overproduction of endolymph may be the dominant causative factor.

Manifestations of Menière’s disease are frequently observed in times of emotional stress in patients with psychological systems under challenge due to a neurasthenic and neurotic psychological profile [10,11]. Mediated through the hypothalamus, stress leads to an increased secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland, followed by an increased adrenocortical production of glucocorticoids (cortisol and corticosterone) and mineralocorticoids (aldosterone) [12]. In animal studies it has been found that elevated aldosterone levels will increase the activity of Na/K-ATP-ase pumps in the stria vascularis of the cochlea and the dark cells of the vestibular labyrinth, resulting in endolymphatic hydrops [13]. The ATP-ase pump regulates the quantity and the composition of the endolymph in the scala media. It seems to be regulated by paracrine and autocrine factors, but, more importantly, also by adrenocorticoid hormones, such as the mineralocorticoid aldosterone. Dunnebier et al. [13] developed a dynamic animal model called the 'Two-phase endolymphatic hydrops'. In this model the absorption of endolymph is chronically disturbed in guinea pigs by surgical dissection of only the distal part of the endolymphatic sac, leaving the intermediate part undamaged. Stimulation of the Na/K-ATP-ase pumps in the stria vascularis of the cochlea and the dark cells of the vestibular labyrinth, resulting in (over)production of endolymph, was established by intraperitoneal administration of aldosterone. The additional influence of endolymph production resulted in an increase in endolymphatic hydrops. Due to the presence of a
borderline destructed sac, the system was probably not capable of maintaining endolymph volume, which resulted in decompensation of the endolymphatic system. In the present study plasma aldosterone assessment was performed in patients with well-defined Menière's disease. It was hypothesized that Menière patients have elevated plasma aldosterone levels compared to non-Menière patients. Differences between Menière and non-Menière patients, as well as differences between unilaterally and bilaterally affected patients, were investigated. Also possible correlations between plasma aldosterone and the duration of the disease, average hearing loss, and the perceived subjective severity of symptoms were studied.

Patients and methods

During a 3.5-year period (from January 1994 to June 1997) 128 patients suspected of having Menière's disease were admitted to the department of Otorhinolaryngology of the University Hospital of Groningen. During their stay in the hospital these patients underwent a wide range of tests, which resulted in a database containing data from routine ENT-examination, questionnaires, audiovestibular tests, routine laboratory investigation, electrocochleography, otoacoustic emission examination and MRI of the temporal bones and cerebellopontine angle. For 106 patients the diagnosis of Meniere’s disease, according to the Definition Menière Groningen was established [8,14]. These patients had a history of vertigo attacks (at least two), suffered or had suffered from tinnitus and had a sensorineural hearing loss of at least 20 dB at one of the pure-tone audiogram frequencies; other pathology was excluded. A detailed discussion of this definition, including the criteria for inclusion and exclusion of patients in the study, is given in chapter 3. Finally, 106 patients diagnosed with Menière's disease, 56 of whom were men (53%) and 50 women (47%), were included in the present study. Sixty-eight patients (64%) had hearing loss and tinnitus in only one ear (unilaterally affected) and 38 patients (36%) had all symptoms in both ears (bilaterally affected). The average age of the patients was 50 years (range 19-77 years), with no significant differences in age between male and female patients or uni- and bilaterally affected patients. Twenty-seven normal individuals, aged 20-30 years, were used as a reference.

Patients were not eligible for the study in the presence of secondary hyperaldosteronism or if any of the following criteria were present: pregnancy, heart failure, a low dietary sodium intake, cirrhosis. The patients with nephrotic syndrome

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1The Definition Menière Groningen differs from the 1995 guidelines of the AAOO-HNS in that it requires the presence of tinnitus instead of leaving the choice between tinnitus and aural fullness. We feel that tinnitus is a more specific symptom than aural fullness.
and peripheral oedema, hypertension (diastolic blood pressure >95 mmHg and systolic diastolic blood pressure >160 mmHg) and/or chronic use of antihypertensive drugs were studied as a separate group [12].

The duration and subjective severity of the symptoms (hearing loss, tinnitus, vertigo and aural fullness) were scored with a standardized questionnaire. The duration of the affection was defined as the period between the first appearance of one of the Menière symptoms and the admission to the University Hospital. For bilaterally affected patients this may lead to different durations in the two ears, if vertigo was not the first symptom. Therefore, the definition of duration of the disease was specified as follows: In unilaterally affected patients this referred to the duration of their affected ear and in bilaterally affected patients to the duration of the disease in the ear which was affected first. The questionnaire on the (subjective) severity of the symptoms attempted to classify the hearing loss, tinnitus, vertigo and the (possible) fullness of the ear, as perceived by the patient during the 3 months before admission. Hearing loss was characterized as 'unchanged', 'improved', 'worse' or 'fluctuating'; tinnitus and aural fullness as 'none', 'mild', 'moderate' or 'severe'; and vertigo as 'absent or instability' or 'severe (attacks lasting > 5 min.)'. Using the duration of the disease, the ears of bilaterally affected patients were characterized as 'affected first' or 'affected last', in those cases where a difference in duration was found in the two ears. Also a distinction between 'most affected' and 'least affected' ears was made for bilaterally affected patients, based on the average hearing loss in the two ears. The average hearing loss was defined as the average hearing thresholds over six pure-tone audiogram frequencies (0.25-8 kHz).

Blood samples for plasma aldosterone assessment were taken in the early morning before breakfast, with the patient in the recumbent position. Plasma aldosterone levels of patients were compared to the plasma aldosterone levels of 27 healthy subjects (aged 20-30 years) and related to the 24-hour urinary sodium excretion [15]. As a rise in plasma aldosterone may be the consequence of an increased renin activity, we measured plasma renin activity (PRA) and computed aldosterone/PRA ratio in a subgroup of 25 patients and in the 27 controls. The PRA and the aldosterone/PRA ratio were also plotted against the 24-hour urinary sodium excretion. Since plasma aldosterone and the plasma renin activity are dependent on sodium intake, patients were put on a standardized sodium diet (130 mmol/24h). To estimate a reliable reference for 24-hour urinary sodium excretion, plasma aldosterone of the controls was measured both on a low (20 mmol/24h) and on a high sodium diet (200 mmol/24h). Sodium and potassium in plasma and urine were measured over 3 days. Twenty-four-hour urinary sodium excretion was computed. To estimate renal function, creatinine levels and urea levels in plasma and urine, as well as the urine volume, were measured. Systolic and diastolic blood pressure were also assessed.

Serum and urinary chemistry were determined with an automated multi-analyzer (SMA-C-ll®, Technicon Instruments Inc., Tarrytown, N.Y., USA). Plasma aldosterone
and PRA were measured by radioimmunoassay [16,17]. PRA was assessed by the quantification of generated angiotensin I as measured by radioimmunoassay (intra-assay variation <7.8%; inter-assay variation <8.2%; lower detection range of 0.15 ng/ml/h).

Statistical analysis was performed with SPSS 10.0 software using mainly descriptive statistics and non-parametric tests (Mann-Whitney U test, Spearman’s correlation, Pearson Chi-square test).

Results

Of the 106 patients, 32 patients were excluded from this study. In 18 of those 32 patients plasma aldosterone levels were not available. Another 14 patients were investigated separately. These patients had hypertension or were using diuretic drugs. Of the 74 non-hypertensive patients, 46 had unilateral and 28 had bilateral Menière's disease. Plasma aldosterone, sodium, potassium and creatinine levels of patients, together with 24-hour urinary sodium excretion, are given in table 1.

Table 1. Plasma aldosterone levels (nmol/l), potassium levels (mmol/l) and creatinine levels (mmol/l). Na in 24-hour urine (mmol/24h). Patients with Menière’s disease (n=74), control group of normal individuals on 200 mmol/24h Na diet (n=27), and excluded hypertensive patients (n=14). SD=standard deviation

<table>
<thead>
<tr>
<th></th>
<th>Plasma aldosterone (nmol/l)</th>
<th>Plasma potassium (mmol/l)</th>
<th>Plasma creatinine (mol/l)</th>
<th>Sodium in 24h urine (mmol/l)</th>
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<tr>
<td></td>
<td>median ±SD</td>
<td>mean ±SD</td>
<td>mean ±SD</td>
<td>mean ±SD</td>
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<tr>
<td>All normotensive patients (n=74)</td>
<td>0.12 ±0.01</td>
<td>0.01-0.77</td>
<td>4.4 ±0.4</td>
<td>87±14.8</td>
</tr>
<tr>
<td>Unilaterally affected patients (n=46)</td>
<td>0.12 ±0.01</td>
<td>0.01-0.77</td>
<td>4.3 ±0.4</td>
<td>86±14.0</td>
</tr>
<tr>
<td>Bilaterally affected patients (n=28)</td>
<td>0.13 ±0.01</td>
<td>0.01-0.49</td>
<td>4.4 ±0.4</td>
<td>87±16.2</td>
</tr>
<tr>
<td>Hypertensive Menière patients (n=14)</td>
<td>0.17 ±0.02</td>
<td>0.02-0.79</td>
<td>4.2 ±0.4</td>
<td>84±15.9</td>
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</tbody>
</table>
Plasma potassium and creatinine of the patients were within the normal range of reference levels that are used at the University Hospital (3.6-4.9 and 62-106 mmol/l, respectively).

The median plasma aldosterone level in the Menière population was 0.12 nmol/l (range 0.01-0.77 nmol/l). When plotting plasma aldosterone against 24-hour sodium excretion, the patients did not have elevated plasma aldosterone compared to controls. If any difference was present, few patients had a plasma aldosterone that was below the borders of the normal range (figure 1).

![Figure 1. Plasma aldosterone levels versus 24-hour urinary sodium excretion in all patients (n=74), in controls on high sodium (200 mmol/24h, n=27), and in the same controls on low sodium (20 mmol/24h) diet. The two dotted lines represent the normal range of the controls.](image)

As a difference in plasma aldosterone may be related to an abnormal PRA, we measured PRA in 25 out of the 74 patients. Plasma aldosterone in this subgroup (n=25), did not differ from the original group (n=74) and was not elevated in the patients (table 2, figure 2a). Three of the 25 patients had a PRA that seemed higher than the normal range; the other subjects had a PRA that was within the normal range.
(table 2, figure 2b). Plasma aldosterone/PRA ratios of these 25 patients were not elevated (figure 2c): all ratios were within the normal range of the controls. No differences in plasma aldosterone level, PRA and plasma aldosterone/PRA ratio were found between uni- and bilaterally affected patients.

**Table 2.** Plasma aldosterone, plasma renin levels, aldosterone/renin ratio’s, potassium and creatinine and 24-hour urinary sodium excretion. Patients with Menière’s disease (n=25), control group of normal individuals with 200 mmol sodium/24h diet (n=27), and excluded hypertensive patients (n=5). SD=standard deviation.

<table>
<thead>
<tr>
<th></th>
<th>plasma aldosterone (nmol/l) median (range)</th>
<th>PRA (nmol/l/h) median (range)</th>
<th>Aldosterone/ PRA ratio median (range)</th>
<th>Potassium in plasma (mmol/l) mean ±SD</th>
<th>Creatinine in plasma (mmol/l) mean ±SD</th>
<th>Na in 24h urine (mmol/l) mean ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>All normotensive patients (n=25)</td>
<td>0.11 (0.01-0.44)</td>
<td>0.40 (0.10-5.00)</td>
<td>0.30 (0.01-1.30)</td>
<td>4.3±0.5</td>
<td>83±12</td>
<td>128±35</td>
</tr>
<tr>
<td>Unilaterally affected patients (n=17)</td>
<td>0.12 (0.01-0.38)</td>
<td>0.40 (0.10-5.00)</td>
<td>0.30 (0.01-1.27)</td>
<td>4.2±0.6</td>
<td>87±11</td>
<td>140±34</td>
</tr>
<tr>
<td>Bilaterally affected patients (n=8)</td>
<td>0.05 (0.01-0.44)</td>
<td>0.35 (0.10-1.10)</td>
<td>0.20 (0.01-1.30)</td>
<td>4.5±0.4</td>
<td>74±9</td>
<td>100±16</td>
</tr>
<tr>
<td>Hypertensive Menière patients (n=5)*</td>
<td>0.18 (0.03-0.80)</td>
<td>0.80 (0.10-5.00)</td>
<td>0.10 (0.03-2.50)</td>
<td>4.0±0.6</td>
<td>83±6</td>
<td>114±39</td>
</tr>
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* On 5 out of 14 hypertensive patients PRA was measured

No correlation was found between plasma aldosterone and the duration of the disease, the duration of vertigo, the presence of tinnitus, aural pressure, or hearing loss. In addition, no significant correlation was found between the plasma aldosterone level and perceived severity of vertigo, tinnitus, aural pressure or hearing loss. Finally, there was no correlation between measured average hearing loss and plasma aldosterone of the patients (n=74). The same results were found for the subgroup of 25 patients in which PRA was measured.
Figure 2a. Plasma aldosterone levels versus 24-hour urinary sodium excretion in all patients of the subgroup in which PRA was measured (n=25), in controls on high sodium (200 mmol/24h, n=27) diet, and in the same controls on low sodium (20 mmol/24h) diet. The two dotted lines represent the normal range of the controls.

b. PRA versus 24-hour urinary sodium excretion in all patients of the subgroup in which PRA was measured (n=25), in controls on high sodium (200 mmol/24h, n=27) diet, and in the same controls on low sodium (20 mmol/24h) diet. The two dotted lines represent the normal range of the controls.
c. Plasma aldosterone/PRA ratio versus 24-hour urinary sodium excretion in all patients of the subgroup in which PRA was measured (n=25), in controls on high sodium (200 mmol/24h, n=27) diet, and in the same controls with low sodium (20 mmol/24h) diet. The two dotted lines represent the normal range of the controls.

The 14 patients with hypertension and/or use of diuretic drugs were studied separately. They had a median plasma aldosterone level of 0.17 nmol/l (range 0.02-0.79), which was not different for the overall group. In 5 of the 14 patients with hypertension PRA was measured. No differences in PRA and the ratio were found between the hypertensive patients and the controls. There was no difference in the duration of the disease between the separately studied hypertensive patients and the included normotensive patients with Menière's disease (Mann-Whitney). There was also no difference in the severity of symptom scores between the excluded hypertensive patients and the 74 normotensive patients with Menière's disease. The average hearing loss in the two groups was equal. No correlation was found with duration or severity of subjective complaints and with average hearing loss. Finally, no differences were found between uni- and bilaterally affected patients.
Discussion

The hypothesis that Menière's disease is associated with elevated plasma aldosterone levels, such as proposed in animal models [13,18], could not be confirmed in this clinical study. A large spread in the data in a relatively small patient cohort was found. When aldosterone levels were plotted against 24-hour urinary sodium excretion (an index for sodium intake) and also when corrected for PRA, no differences in plasma aldosterone were seen between patients and controls. The inability to confirm an elevated plasma aldosterone in patients with Menière’s disease in our study, does not exclude the possibility that a rise in plasma aldosterone may still be found during or shortly before/after an exacerbation of Menière symptoms. The fact that none of our patients suffered an acute attack or exacerbation of their disease during the hospital admission, does not rule out this possibility.

Figure 3. Renin Angiotensin Aldosterone System (RAAS). ECV=extracellular volume, ACTH=adrenocorticotropic hormone, ACE=angiotensin converting enzyme.
It is suggested that an attack of Menière’s disease may be elicited by psychological stress [10,11]. This stress stimulates ACTH secretion, followed by aldosterone secretion in the adrenal cortex, which is a relatively 'fast reacting' process. Generally, plasma aldosterone levels will have returned to normal values after 12 hours [12]. Our patients were admitted to the hospital for 4 days, while the plasma samples were collected on the last day of the admission, early in the morning. Most of the patients experienced a relief of their symptoms and did not suffer from stress at the end of the admission, which could possibly be an explanation for the fact that plasma aldosterone was not found to be elevated.

Under normal conditions an elevated plasma aldosterone level will create a feedback effect in the renin angiotensin aldosterone system (RAAS) (figure 3). This will result in a decrease in plasma renin activity (PRA). When aldosterone is elevated by a factor other than angiotensin II, e.g. ACTH- increase through stress, a high plasma aldosterone level, in combination with a low PRA level, might be expected. In animal studies on Menière’s disease Ten Cate et al. [18] found an increased number of receptors for aldosterone in the stria vascularis of guinea pigs receiving a low sodium diet compared to control guinea pigs receiving a normal sodium diet. In contrast to non-Menière patients, it is possible that our patients, similar to the results of the animal studies just mentioned, also had an increased number of receptors for aldosterone. Following this assumption, even a normal or a slightly elevated plasma aldosterone in a Menière patient could cause an exacerbation of the disease.

The subgroup of patients with hypertension was studied separately because either the diseased condition itself or the drugs used may influence plasma aldosterone. Two types of hypertension can be differentiated. In volume dependent hypertension the extracellular volume is high, which suppresses the renin angiotensin aldosterone system (RAAS), which in turn inhibits the secretion of aldosterone. In volume independent hypertension the RAAS will be stimulated. However, plasma aldosterone levels were normal and did not differ from the plasma levels of the 74 normotensive patients. There was no difference in the duration of the disease between the excluded hypertensive patients and the included normotensive patients. Also, no difference in the perceived severity of subjective symptoms between hypertensive and normotensive patients was found.

In Menière's disease it is hypothesized that a possible increase in plasma aldosterone level might be caused by an increase in ACTH and not by a disorder of the RAAS itself. An increase in ACTH also results in an increase in glucocorticoids like cortisol. The ACTH release is sensitive to the circulating blood level of glucocorticoids. When such blood levels are increased in the normal individual, less ACTH is released from the anterior pituitary gland and less steroids are produced by the adrenal gland [12]. In depressive patients, chronic stress results in persistently high cortisol blood levels as a result of a disturbed feedback mechanism [19,20]. An identical defect in the central regulation system could be operational in Menière’s disease.
Conclusion

No anomalous plasma aldosterone levels were found in Menière patients during an attack-free period. The question whether plasma aldosterone and cortisol levels show variations before, during and after an attack, remains to be answered. If so, this might contribute to a better understanding of the pathophysiological mechanism of Menière’s disease.

References


