Plasma Metanephrines in the Diagnosis of Pheochromocytoma

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**Objective:** To examine whether tests for plasma metanephrines, the α-methylated metabolites of catecholamines, offer advantages for diagnosis of a pheochromocytoma over standard tests for plasma catecholamines or urinary metanephrines.

**Design:** Cross-sectional study.

**Setting:** 3 clinical specialist centers.

**Patients:** 52 patients with a pheochromocytoma; 67 normotensive persons and 51 patients with essential hypertension who provided reference values; and 23 patients with secondary hypertension and 50 patients with either heart failure or angina pectoris who served as comparison groups.

**Measurements:** Plasma concentrations of catecholamines (norepinephrine and epinephrine) and metanephrines (normetanephrine and metanephrine) were measured in all patients. The 24-hour urinary excretion of metanephrines was measured in 46 patients with pheochromocytoma.

**Results:** Pheochromocytomas were associated with increases in plasma concentrations of metanephrines that were greater and more consistent than those in plasma catecholamine concentrations. No patient with a pheochromocytoma had normal plasma concentrations of both normetanephrine and metanephrine. The sensitivity of these tests was 100% (52 of 52 patients [95% CI, 94% to 100%]), and the negative predictive value of normal plasma concentrations of metanephrines was 100% (162 of 162 patients). Tests for plasma catecholamines yielded eight false-negative results and a sensitivity of 85% (44 of 52 patients [CI, 72% to 93%]). The negative predictive value of normal plasma concentrations of catecholamines was 95% (156 of 164 patients). Tests for urinary metanephrines yielded five false-negative results and a sensitivity of 89% (41 of 46 patients [CI, 76% to 96%]). Because no statistical difference was noted in the number of false-negative results between tests for plasma metanephrines (15%) and tests for plasma catecholamines (18%), the specificities of the two tests did not differ.

**Conclusions:** Normal plasma concentrations of metanephrines exclude the diagnosis of pheochromocytoma, whereas normal plasma concentrations of catecholamines and normal urinary excretion of metanephrines do not. Tests for plasma metanephrines are more sensitive than tests for plasma catecholamines or urinary metanephrines for the diagnosis of pheochromocytoma.


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why a test for vanillylmandelic acid is also a poorer marker for pheochromocytoma than other tests (17). In contrast, preferential metabolism of circulating catecholamines compared with neuronal catecholamines by extraneuronal pathways (14) suggests that the metanephrines—as extraneuronal metabolites—may provide good markers for release of catecholamines from a pheochromocytoma. Furthermore, substantial production of metanephrines within adrenal tissue (18) suggests that metanephrines may be produced within the tumor itself.

In humans, metanephrines are extensively sulfate-conjugated (18, 19). Assays of metanephrines in urine depend on measurements after deconjugation to free metanephrines (19) so that measurements represent the sum of free and conjugated metabolites (total metanephrines). In contrast, good sensitivity of the assay for plasma metanephrines (20) enables measurements of both free and total metanephrines.

We compared the sensitivity, specificity, and positive and negative predictive values of tests for plasma free and total metanephrines with those of tests for plasma catecholamines and urinary total metanephrines. Study participants included a relatively large sample of patients with pheochromocytoma, patients with essential hypertension or secondary hypertension from causes other than pheochromocytoma, and patients with either heart failure or angina pectoris in whom sympathetically mediated catecholamine release would be expected to be increased.

Methods

Patients

Fifty-two patients with a histologically proven pheochromocytoma were studied. Thirty patients were studied retrospectively, and 22 were studied before the final diagnosis was made. The pheochromocytoma was benign in 39 patients and malignant in 13. Sixty-seven healthy, normotensive persons and 51 patients with either heart failure or angina pectoris. The age, sex, and specialty center where the patients were studied for each of the five groups are shown in Table 1. Except for the few patients who were being treated with phenoxybenzamine, no patients with pheochromocytoma had been receiving medication for at least 2 weeks at the time of blood sampling. No patients with essential hypertension had been receiving medication for at least 2 weeks at the time of blood sampling. Medications taken by the other patient groups included digoxin, calcium channel blockers, diuretics, acetylsalicylic acid, dipyriramole, and cyclosporine. Procedures used in our study were approved by the hospital ethics committee or intramural research board of each of the three centers where patients were studied.

Blood and Urine Samples

All patients refrained from ingesting methylxanthine-containing food products and from smoking after midnight on the day before blood sampling. Blood was collected from an indwelling catheter in an antecubital vein after the patients had rested supine for 20 minutes. In 39 patients with heart failure and 15 with secondary hypertension, arterial blood was obtained through an indwelling arm arterial catheter. Blood samples were collected into precooled tubes containing heparin or EGTA and glucose and were centrifuged within 30 minutes to separate the plasma, which was stored frozen until assayed. All plasma catecholamine and urinary metanephrine assays were done within 2 weeks of sample collection. Seven of the 52 pheochromocytoma samples were assayed for plasma metanephrines after being stored at −80°C for more than 2 years (range, 3 to 8 years), whereas the remaining 45 samples were assayed within 2 years of collection (22 samples within 4 weeks). In 46 of the 52 patients with pheochromocytoma, a 24-hour urine collection was obtained, with 30 mL of 6-M hydrochloric acid used as a preservative.

Analytic Methods

Plasma metanephrines were assayed at the National Institutes of Health (NIH) using liquid chromatography with electrochemical detection (20). Concentrations of total metanephrines (the sum of concentrations of free and sulfated conjugated metanephrines) were measured after incubation of 0.25 mL of plasma with 0.1 units of sulfatase (Sigma Chemical Company, St. Louis, Missouri) at 37°C for 30 minutes. The detection limits were 0.013 nmol/L for normetanephrine and 0.019 nmol/L for metanephrine. At a plasma normetanephrine concentration of 0.31 nmol/L and a metanephrine concentration of 0.21 nmol/L, the interassay coefficients of variation were 12.2% for normetanephrine and 11.2% for metanephrine. As previously reported (20), the presence of acetaminophen in samples of plasma can substantially interfere with measurements of plasma normetanephrine concentrations. Therefore, this analgesic must not be used by patients for several days before blood samples are collected. No analytic interference of various other drugs with this assay has been shown (20). Plasma catecholamines were assayed using liquid chromatography. Electrochemical detection was used for quantification at the NIH (21), and fluorometric detection was used at St. Radboud University Hospital, Nijmegen, the Netherlands (22). At the NIH, the detection limits were 0.006 nmol/L for normepinephrine and 0.010 nmol/L for epinephrine. At a plasma norepinephrine concentration of 2.4 nmol/L and an epinephrine concentration of 0.39 nmol/L, the interassay coefficients of variation were 6.5% for norepinephrine and 11.4% for epinephrine. At St. Radboud University Hospital, the detection limits for norepinephrine and epinephrine were 0.002 nmol/L and 0.003 nmol/L, respectively. At plasma concentrations of 1.02 nmol/L for norepinephrine and 0.15 nmol/L for epinephrine, interassay coefficients of variation were 8.5% for norepinephrine and 7.2% for epinephrine.

Urinary concentrations of metanephrines were measured according to a previously described method (23); the upper reference limit of the normal range for the 24-hour urinary output of metanephrines was 6.8 μmol/d.

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Table 1. Patient Characteristics*  

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotension</th>
<th>Essential Hypertension</th>
<th>Secondary Hypertension</th>
<th>Heart Failure or Angina Pectoris</th>
<th>Pheochromocytoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>67</td>
<td>51</td>
<td>23</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td>Mean age ± SD (range), y</td>
<td>39 ± 12 (20–72)</td>
<td>43 ± 13 (16–69)</td>
<td>48 ± 14 (20–69)</td>
<td>57 ± 11 (34–81)</td>
<td>39 ± 13 (11–71)</td>
</tr>
<tr>
<td>Male/female, n/n</td>
<td>40/27</td>
<td>24/27</td>
<td>14/9</td>
<td>42/8</td>
<td>28/24</td>
</tr>
<tr>
<td>Study center (NIH/SR/SH), n/n/n</td>
<td>36/31/0</td>
<td>1/50/0</td>
<td>17/15</td>
<td>13/7/30</td>
<td>41/11/0</td>
</tr>
</tbody>
</table>

* NIH = National Institutes of Health; SH = Sahlgrens Hospital; SR = St. Radboud University Hospital.
Because plasma concentrations of catecholamines and metanephrines were not normally distributed, only medians and ranges are presented for these concentrations. Differences in plasma concentrations of metanephrines and catecholamines among patients with pheochromocytoma and other groups were tested using the Kruskal-Wallis test. We assessed relations among variables using the Spearman rank correlation coefficient.

Normal distributions of plasma concentrations of catecholamines and metanephrines were obtained after logarithmic transformation of the data. Thus, upper reference limits, defined as the 97.5th percentile, were determined after logarithmic transformation of individual values for the combined data from normotensive persons and those with essential hypertension (118 persons). The 97.5th percentiles were calculated from the anti-logarithm of the mean plus 2 standard deviations of the transformed data. A false-negative result of a test for plasma metanephrines in a patient with pheochromocytoma was defined as plasma concentrations of both normetanephrines and metanephrines that were below their respective upper reference limits. Similarly, a false-negative result of a test for plasma catecholamines was defined as plasma concentrations of norepinephrine and epinephrine that were below their respective upper reference limits. A false-positive result of a test for plasma metanephrines was defined as plasma concentrations of either normetanephrine or metanephrine that was equal to or greater than the upper reference limits. We calculated the sensitivity and specificity (with 95% CIs), pretest and post-test probabilities, and positive and negative predictive values for each analyte (24).

Differences in tumor-associated elevations in plasma catecholamine concentrations and free and total metanephrine concentrations were assessed from the fold-increases in plasma concentrations of compounds in patients with pheochromocytoma that were greater than median values in the normotension and essential hypertension reference group. We computed mean ± SE fold-increases after logarithmic transformation of individual fold-increases. We estimated differences among fold-increases by analysis of variance; post hoc tests were done with the Scheffe F-test.

Receiver-operating characteristic curves were constructed from the relation between the rates of true-positive and false-positive results (that is, sensitivity compared with 1 minus the specificity) for diagnosis of pheochromocytoma that are based on different upper reference limits for each analyte (25). These curves enabled us to compare the sensitivity and specificity of tests for plasma metanephrines for diagnosing pheochromocytoma with those of tests for plasma catecholamines, as a function of different upper reference limits for each analyte. The areas under the receiver-operating characteristic curves for plasma catecholamines and metanephrines were calculated as summary measures of the diagnostic power that were independent of upper reference limits. We calculated the difference between the two areas and tested them according to the method of Hanley and McNeil (26).

Results

Plasma Concentrations of Catecholamines and Free and Total Metanephrines

Plasma concentrations of free normetanephrine and metanephrine in the normotension and hypertension reference groups were not normally distributed until the data were logarithmically transformed (Figure 1). Ranges of plasma concentrations of nor- and metanephrine were wider and the values were considerably higher (P < 0.001) in patients with pheochromocytoma than in any other patient group (Table 2).

In each group, plasma concentrations of total meta-
However, this patient (patient 42; Table 3) also had an elevated plasma metanephrine concentration. Thus, when both metabolites were considered in the diagnosis rather than plasma normetanephrine alone, the number of false-negative results was reduced from 1 to 0, yielding a sensitivity and negative predictive value of 100% (Table 4). In 29 of the 191 patients (15%) without pheochromocytoma, a test for plasma normetanephrine or metanephrine yielded a false-positive result (Figure 2). Six of these 29 false-positive results were obtained in patients with renal artery stenosis or renal failure, and 16 were obtained in patients with heart failure.

Accuracy of Tests for Plasma Catecholamines

The upper reference limits were 3.00 nmol/L for norepinephrine and 0.54 nmol/L for epinephrine. In contrast to the one patient with pheochromocytoma and a false-negative result of the plasma normetanephrine test, 10 patients had false-negative plasma norepinephrine test results (Figure 2, top). Of these 10 patients, 2 had elevated plasma epinephrine concentrations (patients 32 and 34; Table 3); thus, the number of false-negative results was reduced from 10 to 8 when the diagnosis was based on plasma concentrations of both norepinephrine and epinephrine rather than on norepinephrine concentrations alone. This resulted in a sensitivity of 85% (Table 4). Tests of plasma catecholamines yielded false-positive results in 35 (18%) of the 191 patients without pheochromocytoma (Figure 2). In 19 of these 35 patients, results of tests for plasma metanephrines were also false-positive. Seven of these 35 false-positive results were obtained in patients with renal artery stenosis or renal failure, and 21 were obtained in patients with heart failure.

Accuracy of Tests for Urinary Metanephrines

Twenty-four-hour urine specimens were obtained from 46 of the 52 patients with pheochromocytoma and were not obtained from patients in any other group. The median urinary excretion rate of metanephrines in these patients was 24.2 μmol/d (range, 2.1 to 242 μmol/d). Use of an upper reference limit of 6.8 μmol/d for the urinary excretion of metanephrines in normotensive persons (23) yielded false-negative results in 5 of the 46 patients and a sensitivity of 89% (95% CI, 76% to 96%); all 5 patients had increased plasma concentrations of metanephrines, but only 3 had increased plasma concentrations of catecholamines. Creatinine excretion among the 5 patients with normal urinary excretion of metanephrine was within the normal range (1 to 2.5 g/d). Use of an upper reference limit of 9.5 μmol/d in hypertensive patients (4)
yielded 10 false-negative results and a sensitivity of 78% (CI, 64% to 89%).

Accuracy of Tests for Plasma Metanephrines Compared with Tests for Catecholamines

Tumor-associated elevations in plasma normetanephrine concentrations were 153% greater than those in plasma norepinephrine and 64% greater than those in plasma concentrations of total normetanephrine (Figure 3, top). Tumor-associated elevations in plasma metanephrine concentrations were 70% greater than those in epinephrine concentrations but did not differ from those in total metanephrine concentrations (Figure 3, bottom). Increases in plasma concentrations of total normetanephrine were 54% greater than increases in plasma concentrations of norepinephrine, whereas increases in total metanephrine concentrations were 46% greater than increases in epinephrine concentrations.

Among the 11 patients with pheochromocytoma and equivocal results of tests for normetanephrine or norepinephrine (Table 3), 17 positive results were obtained for tests for metanephrines (normetanephrine, 10 results; metanephrine, 7 results); only 4 positive results were obtained for tests for catecholamines (norepinephrine, 1 result; epinephrine, 3 results). In 7 of these 11 patients, plasma normetanephrine or metanephrine concentrations were elevated more than three times the upper reference limits for metanephrines; no patients had elevations in plasma norepinephrine or epinephrine concentrations greater than three times the respective upper reference limits.

Receiver-operating characteristic curves, which show the relation between rates of true-positive and false-positive results at different decision thresholds (that is, at different upper reference limits of plasma concentrations of metanephrines and catecholamines), confirmed the superiority of tests for plasma metanephrines over tests for plasma catecholamines for the diagnosis of pheochromocytoma, regardless of the reference limits used to define an abnormal test result (Figure 4, top). The area under the curve for plasma metanephrines (0.977 ± 0.015) was greater than that for plasma catecholamines (0.917 ± 0.027) (P = 0.03).

The relation between pretest and post-test probabilities—estimated from the sensitivity and specificity values listed in Table 4—show that as the prevalence rate (that is, the pretest probabilities) increases, the post-test probabilities similarly increase for diagnoses that are based on plasma concentrations of metanephrines and catecholamines (Figure 4, bottom). The negative predictive value of tests for plasma metanephrines for the diagnosis of pheochromocytoma remained constant at 100% for all prevalence rates, whereas the negative predictive value of

Table 3. Neurochemical Characteristics of 11 Patients with Pheochromocytoma and Normal (False-Negative) Plasma Concentrations of Norepinephrine or Normetanephrine

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical Syndrome</th>
<th>Norepinephrine</th>
<th>Epinephrine</th>
<th>Normetanephrine</th>
<th>Metanephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Sporadic</td>
<td>2.80</td>
<td>0.20</td>
<td>1.03*</td>
<td>0.28</td>
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<tr>
<td>21</td>
<td>Sporadic</td>
<td>2.90</td>
<td>0.36</td>
<td>3.39*†</td>
<td>1.13*†</td>
</tr>
<tr>
<td>27</td>
<td>Sporadic</td>
<td>0.69</td>
<td>0.53</td>
<td>1.98*†</td>
<td>0.37*†</td>
</tr>
<tr>
<td>32</td>
<td>Sporadic</td>
<td>2.93</td>
<td>0.93*</td>
<td>4.38*†</td>
<td>2.31*†</td>
</tr>
<tr>
<td>34</td>
<td>Sporadic</td>
<td>1.73</td>
<td>1.26*</td>
<td>17.19*†</td>
<td>16.52*†</td>
</tr>
<tr>
<td>38</td>
<td>Sporadic</td>
<td>2.42</td>
<td>0.17</td>
<td>9.44*†</td>
<td>0.21</td>
</tr>
<tr>
<td>42</td>
<td>Cushing</td>
<td>4.21*†</td>
<td>1.61*</td>
<td>0.48</td>
<td>0.55*</td>
</tr>
<tr>
<td>43</td>
<td>von Hippel-Lindau</td>
<td>2.08</td>
<td>0.03</td>
<td>1.69</td>
<td>0.06</td>
</tr>
<tr>
<td>48</td>
<td>Multiple endocrine neoplasia</td>
<td>1.83</td>
<td>0.21</td>
<td>4.10*†</td>
<td>1.40**</td>
</tr>
<tr>
<td>49</td>
<td>Multiple endocrine neoplasia</td>
<td>1.74</td>
<td>0.32</td>
<td>1.28*</td>
<td>3.85**</td>
</tr>
<tr>
<td>50</td>
<td>von Hippel-Lindau</td>
<td>2.43</td>
<td>0.04</td>
<td>1.71*</td>
<td>0.18</td>
</tr>
<tr>
<td>Upper reference limit</td>
<td></td>
<td>3.00</td>
<td>0.54</td>
<td>0.66</td>
<td>0.30</td>
</tr>
</tbody>
</table>

* Denotes a concentration above the upper reference limits.
† Denotes a concentration more than threefold above the upper reference limits.

Table 4. Characteristics of Tests for Plasma Metanephrines and Catecholamines

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>% (n/n)</td>
<td></td>
</tr>
<tr>
<td>Metanephrines*</td>
<td>100 (52/52) (94 to 100)</td>
<td>85 (162/191) (79 to 90)</td>
<td>64 (52/81)</td>
<td>100 (162/162)</td>
</tr>
<tr>
<td>Total metanephrines</td>
<td>98 (42/43) (68 to 100)</td>
<td>82 (112/137) (74 to 88)</td>
<td>63 (42/67)</td>
<td>99 (112/113)</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>85 (44/52) (72 to 93)</td>
<td>82 (156/191) (75 to 87)</td>
<td>56 (44/79)</td>
<td>95 (156/164)</td>
</tr>
</tbody>
</table>

* “Metanephrines” refers to free normetanephrine and metanephrine. “Total metanephrines” refers to sulfated conjugated and free normetanephrine and metanephrine. The sensitivity of (total) metanephrines for diagnosis of pheochromocytoma was calculated from patients with both a false-negative plasma (total) normetanephrine test result and a false-negative (total) metanephrine test result. The specificity of catecholamines was calculated from patients with either a false-positive plasma (total) norepinephrine test result or a false-positive (total) metanephrine test result. The specificity of catecholamines was calculated from patients with either a false-positive plasma norepinephrine test result or a false-positive plasma epinephrine test result.
tests for plasma catecholamines decreased with increasing prevalence rates.

In terms of positive and negative predictive values, measurement of plasma concentrations of total normetanephrine and metanephrine provided no advantage over measurement of free metanephrine concentrations (Table 4). However, measurements of plasma concentrations of total metanephrines provided greater sensitivity for the diagnosis of pheochromocytoma than measurements of plasma concentrations of catecholamines.

Discussion

Because a pheochromocytoma secretes catecholamines directly into the circulation, any of several means to detect the tumor by assays of plasma or urinary catecholamines and their metabolites should theoretically prove adequate. However, the occurrence of false-nega-
The relation between pretest probability (that is, prevalence) and post-test probability shows the effect of prevalence of pheochromocytoma and plasma catecholamines. Curves were constructed from estimates of the true-positive (sensitivity) and false-positive (1 - specificity) rates obtained using upper reference limits determined from the mean plus 1, 1.5, 2.0, 2.5, 3.0, or 3.5 SDs. The different upper reference limits (nmol/L) for plasma catecholamines and metanephrines are tabulated below:

<table>
<thead>
<tr>
<th>Catecholamines</th>
<th>Metanephrines</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normetanephrine</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>1.93</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>1.18</td>
</tr>
<tr>
<td></td>
<td>1.76</td>
</tr>
</tbody>
</table>

The negative predictive value of normal plasma concentrations of metanephrines was superior to that of normal plasma catecholamines regardless of prevalence rates (Figure 3, bottom), a disparity that increased with increasing prevalence. Even at the highest prevalence rates, normal plasma concentrations of metanephrines almost exclude diagnosis of pheochromocytoma. This means that in a general practice setting or in patients in whom pheochromocytoma is strongly suspected (for example, patients at a referral center who have hypertension, headache, and adrenal mass), normal plasma concentrations of metanephrines may exclude the diagnosis of pheochromocy-
concentrations. It is the free, not the conjugated, metanephrines rules out this explanation. Another possibility is that the assay technique used (23) is a determinant of metabolite production but not of catecholamines. Therefore, plasma concentrations of metanephrines may be particularly useful for excluding pheochromocytoma in patients with a panic disorder.

Greater and more consistent tumor-associated increases in plasma concentrations of metanephrines than in catecholamine concentrations explain the better sensitivity of the test for the former for diagnosing pheochromocytoma. The production of 90% of plasma metanephrines and as much as 40% of plasma normetanephrine from metabolism of catecholamines within the adrenal glands (18, 29) suggests that metanephrines are produced within the tumor itself. This conclusion is supported by observations of high tumor-tissue concentrations of metanephrines (30, 31) and high plasma normetanephrine concentrations in the venous effluent of pheochromocytomas (32). The conclusion is also supported by our findings reported here and elsewhere (33) that tumor size is a determinant of metabolite production but not of catecholamine release. Thus, even when pheochromocytomas are quiescent and are not releasing catecholamines, they appear to be actively metabolizing catecholamines to metanephrines.

Our results confirm the high sensitivity and specificity of tests for plasma total metanephrines for the diagnosis of pheochromocytoma that has been shown previously (34); however, only concentrations of total metanephrines were considered in that study. We found that measurement of total (unconjugated and conjugated) metanephrines had no advantage over measurement of free (unconjugated) metanephrines. Rather, the presence of a tumor causes relatively larger increases in free normetanephrine concentrations than in total normetanephrine concentrations. It is the free, not the conjugated, metanephrines that are produced within chromaffin tissue (unpublished observations). Thus, although plasma concentrations of total metanephrines are technically easier to measure than plasma concentrations of free metanephrines, the latter yield superior results.

In conclusion, normal plasma concentrations of metanephrines were considered in that study. We found that measurement of total (unconjugated and conjugated) metanephrines were considered in that study. We found that measurement of total (unconjugated and conjugated) metanephrines.
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References