Vascular damage and dysfunction in hypertensive emergencies
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Value of retinal examination in hypertensive encephalopathy

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Chapter 4

ABSTRACT

The presence of grade III or IV hypertensive retinopathy (HRP) is considered to distinguish hypertensive urgencies from emergencies. However, case-reports suggest that these retinal changes may be lacking in patients with hypertensive encephalopathy. To assess the frequency of grade III and IV retinopathy in this hypertensive emergency, we conducted a retrospective cohort study. We retrieved 162 patients with malignant hypertension and 34 patients (17%) fulfilled the predefined criteria for hypertensive encephalopathy. Data on retinal examination were incomplete for 6 patients (18%), thus leaving 28 patients who were analysed for the presence or absence of grade III and IV HRP. In 9 (32%) patients with hypertensive encephalopathy, grade III or IV HRP was absent, 11 (39%) patients presented with grade III and 8 (29%) patients with grade IV retinopathy. Patients without retinal abnormalities were on average 13 years younger (P=0.05), more often black (P=0.02) and displayed lower blood pressure (BP) values (P=0.04 for systolic and diastolic BP). A substantial proportion of patients with hypertensive encephalopathy lack grade III or IV HRP. This suggests that the decision to admit these patients should not only rely on the presence of grade III and IV retinopathy alone, but should also include a careful neurological examination.
INTRODUCTION

Since 1939 the Keith, Wagener and Barker classification is used to assess retinal changes associated with hypertension. At that time, they observed a remarkably high mortality among patients presenting with grade III and IV hypertensive retinopathy (HRP), with 65% of patients having grade III retinopathy and more than 90% of patients having grade IV deceased after 1 year. The introduction of effective antihypertensive treatment has dramatically improved prognosis of patients presenting with malignant hypertension. In the 1980s no difference in survival was observed between patients presenting with grade III and IV HRP. Since, both grade III and IV HRP are included to define patients with malignant hypertension.

Malignant hypertension is a heterogeneous disorder, recognition of a true hypertensive emergency can therefore be difficult. A retinal examination can be helpful as the presence of grade III or IV HRP by definition indicates a hypertensive emergency. Hypertensive encephalopathy is present in 15 to 20% of patients who present with malignant hypertension. Hypertensive encephalopathy is a life-threatening disorder characterized by severe hypertension and neurological manifestations including lowered consciousness, lethargy, confusion, blindness and seizures in the absence of other causes. Symptoms occur when blood pressure rises above cerebral autoregulation limits. For the treatment of hypertensive encephalopathy, a controlled reduction of blood pressure is mandated to prevent hyper- and hypoperfusion of the brain resulting from impaired cerebral autoregulation.

Previous case-reports have shown however, that the ischemic retinal lesions corroborating malignant hypertension may be lacking in patients with hypertensive encephalopathy. To assess the frequency of retinal abnormalities consistent with grade III and IV HRP, we conducted a retrospective cohort study of patients admitted with hypertensive encephalopathy in the past 16 years.

METHODS

Participants and setting

Retrospective analysis was carried out using the hospital database in which the diagnosis at discharge is recorded according to the International Classification of Diseases codes (ICD). All charts of patients admitted at a large teaching hospital (Academic Medical Center in Amsterdam) between August 1992-July 2008 with the diagnosis ‘hypertensive encephalopathy’ (ICD 437.2), ‘essential malignant hypertension’ (ICD 401.0), ‘secondary malignant hypertension’ (ICD 405.09), ‘hypertension with cardiac disease/ malignant’ (ICD 402.0) and ‘hypertension with kidney disease/malignant’ (ICD 403.0) were reviewed. To
identify the presence of registration errors, computer data of all patients discharged with
the diagnosis ‘essential hypertension’ (ICD 401.9) were also analyzed which showed the
presence of one patient with malignant hypertension.
Selection bias could be introduced if patients with hypertensive encephalopathy and without
retinal changes were discharged from the emergency department without being admitted.
Therefore a sensitivity analysis was carried out by searching the emergency room archives
for patients fulfilling the clinical criteria for hypertensive encephalopathy in a sample of
3 different years, with each year randomly selected from a period of 5 consecutive years.
Patients referred from elsewhere were excluded to prevent selection bias.

Procedure
Ophthalmologists performed a retinal examination by direct fundoscopy following
appropriate mydriasis with Tropicamide (0.5%) and Phenylephrine (2.5%). Neurologists
did not routinely dilate pupils before performing a retinal examination. All patients were
examined within 24 hours of admission.

Data collection
Two clinicians, blinded for the results of the retinal examination, independently reviewed
charts of patients to assess the presence of predefined clinical criteria for hypertensive
encephalopathy. Clinical criteria include: 1) diastolic blood pressure (BP) ≥120 mmHg and the
presence of at least one of the following: acute or subacute onset of lowered consciousness,
lethargy, confusion, seizures or cortical blindness; 2) resolution of these symptoms after
blood pressure lowering treatment; 3) no other explanation for the neurological symptoms
at presentation.10 Definitive diagnosis in case of disagreement between the clinicians was
made after discussion.
All patients with hypertensive encephalopathy who received a retinal examination at
admission were included. Hypertensive retinopathy was classified according to the original
Keith, Wagener and Barker classification with grade I representing slight or modest
narrowing of retinal arterioles (arteriovenous ratio ≥ 1:2), grade II - modest to severe
narrowing of retinal arterioles (focal or generalized), with an arteriovenous ratio <1:2 or
arteriovenous nicking. Grade III - bilateral soft exudates or flame shaped hemorrhages, and
grade IV - bilateral optic nerve edema (with or without grade III abnormalities).1 Excluded
from analysis were patients <19 years of age and pregnant women.

Statistical analysis
Patients characteristics were described using numbers and percentages, mean and SD
or median and interquartile range for variables with a skewed distribution. Between
group differences were assessed by t-test for parametric and Mann-Whitney U test for
nonparametric distributions. Chi-square analysis was used for categorical variables. Sensitivity with 95% confidence interval [CI] and false negative rate was used to reflect the diagnostic accuracy of retinal findings for diagnosing hypertensive encephalopathy. For statistical analyses SPSS (Statistical Package for the Social Sciences) software for Windows was used, version 14.0 (SPSS Inc., Chicago, Illinois, USA). P values were considered to indicate a significant difference if P < 0.05.

RESULTS

A total amount of 162 patients could be identified who fulfilled the WHO criteria for malignant hypertension, but had no clinical characteristics consistent with hypertensive encephalopathy. Based on predefined clinical criteria the diagnosis hypertensive encephalopathy could be made in 34 (17%) patients (Table 1). In 7 (21%) of these patients agreement on definitive diagnosis was reached after discussion by two clinicians. This led to the inclusion of five patients and exclusion of two patients. In 6 (18%) cases of hypertensive encephalopathy no or incomplete data on retinal examination were available, mainly because of the fact that only the presence or absence of optic nerve oedema was described, leaving 28 patients with hypertensive encephalopathy and complete description of the retina for further analysis (Figure 1). Sensitivity analysis revealed that no patients with hypertensive encephalopathy lacking retinal changes were discharged from the emergency department.

Table 1. Distribution of inclusion criteria in all patients admitted with hypertensive encephalopathy and comparison of groups with and without grade III or IV hypertensive retinopathy

<table>
<thead>
<tr>
<th>Clinical manifestations*</th>
<th>Total (34)</th>
<th>Grade III or IV present (19)</th>
<th>Grade III or IV absent (9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td>18 (53%)</td>
<td>7 (37%)</td>
<td>6 (67%)</td>
</tr>
<tr>
<td>Lowered consciousness</td>
<td>6 (18%)</td>
<td>4 (21%)</td>
<td>0</td>
</tr>
<tr>
<td>Delirium</td>
<td>4 (12%)</td>
<td>4 (21%)</td>
<td>0</td>
</tr>
<tr>
<td>Lethargy</td>
<td>8 (24%)</td>
<td>6 (32%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>Confusion</td>
<td>8 (24%)</td>
<td>6 (32%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>Cortical blindness</td>
<td>2 (6%)</td>
<td>1 (5%)</td>
<td>1 (11%)</td>
</tr>
</tbody>
</table>

Values are numbers and percentages.

* Some patients presented with more than one of these symptoms at presentation. Headache, blurred vision, nausea and vomiting are often seen in patients with malignant hypertension but are not specific for hypertensive encephalopathy and are left out in this table.
Chapter 4

Figure 1. Patient selection

ICD indicates International Classification of diseases

Retinal examination was mainly carried out by ophthalmologists and in a few cases by neurologists (Table 2). In total, 9 patients out of 28 patients with hypertensive encephalopathy (32%) lacked retinal abnormalities consistent with grade III and IV HRP, 7 (25%) patients having normal retinal findings. In the other 19 patients, grade III HRP was present in 11 patients (39%) and grade IV HRP in 8 (29%) patients (Table 2). Sensitivity of retinal examination in hypertensive encephalopathy could therefore be estimated at 68% (95% confidence interval 49–82%). Patients who presented without grade III or IV HRP were on average 13 years younger (P=0.05), were more often black (P=0.02) and displayed lower BP values at admission compared with those who presented with grade III or IV HRP (Table 3).

Table 2. Hypertensive retinopathy in patients with hypertensive encephalopathy reported by either ophthalmologists or neurologists.

<table>
<thead>
<tr>
<th>Hypertensive retinopathy</th>
<th>Patients</th>
<th>Ophthalmologists</th>
<th>Neurologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>7 (25%)</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Choroidopathy</td>
<td>1 (4%)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Grade II</td>
<td>1 (4%)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Grade III</td>
<td>11 (39%)</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Grade IV</td>
<td>8 (29%)</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>28 (100%)</td>
<td>22</td>
<td>4</td>
</tr>
</tbody>
</table>

Values are numbers and percentages.
Data on who performed retinal examination could not be retrieved for 2 patients.
Retinal Examination in Hypertensive Encephalopathy

Table 3. Clinical characteristics of patients admitted with hypertensive encephalopathy and comparison of groups with and without grade III or IV hypertensive retinopathy.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Grade III or IV present</th>
<th>Grade III or IV absent</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>19 (68%)</td>
<td>9 (32%)</td>
<td></td>
</tr>
<tr>
<td>Age, yrs (mean ± SD)</td>
<td>50 ± 18</td>
<td>37 ± 9</td>
<td>0.05</td>
</tr>
<tr>
<td>Male</td>
<td>5 (26%)</td>
<td>4 (44%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Black</td>
<td>5 (26%)</td>
<td>7 (78%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Systolic BP, mmHg (mean ± SD)</td>
<td>242 ± 29</td>
<td>215 ± 29</td>
<td>0.04</td>
</tr>
<tr>
<td>Diastolic BP, mmHg (mean ± SD)</td>
<td>146 ± 19</td>
<td>133 ± 12</td>
<td>0.04</td>
</tr>
<tr>
<td>Serum creatinine, μmol/l (median, [IQR])</td>
<td>326 [94-513]</td>
<td>129 [68-1048]</td>
<td>0.47</td>
</tr>
<tr>
<td>Macroalbuminuria†</td>
<td>9 (47%)</td>
<td>3 (33%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>13 (68%)</td>
<td>4 (44%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Previous hypertension</td>
<td>12 (63%)</td>
<td>6 (66%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>1 (58%)</td>
<td>15 (55%)</td>
<td>0.91</td>
</tr>
<tr>
<td>Incompliance with medication</td>
<td>6 (32%)</td>
<td>3 (33%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Secondary hypertension</td>
<td>6 (32%)</td>
<td>4 (44%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Current smoker‡</td>
<td>6 (32%)</td>
<td>1 (11%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Diabetes Mellitus§</td>
<td>3 (15%)</td>
<td>1 (11%)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Values are numbers and percentages unless stated otherwise. IQR indicates interquartile range.

* P values calculated for differences between HE patients with and without grade III or IV HRP.
† Data missing for 3 in those with grade III or IV HRP and for 2 in those without.
‡ Data missing for 2 in those with grade III or IV HRP and for 1 in those without.
§ Data missing for 1 in both groups.

Data on retinal examination were incomplete for 6 patients, 5 of these patients were male and 2 of them were black. The mean age of those with an incomplete retinal examination was 44±20 years and mean BP was 232±20 systolic and 137±13 diastolic. Median serum creatinine was 511 with an interquartile range between 93 and 774. In 4 of the 34 patients, additional risk factors for encephalopathy could be identified besides severe hypertension. These included three patients with HIV using antiretroviral therapy and one patient receiving cyclosporine next to prednisone after renal transplantation. All these patients had retinal changes consistent with grade III or IV HRP.

DISCUSSION

In the present study, we found that 32% of patients who fulfilled the predefined criteria of hypertensive encephalopathy lacked retinal abnormalities consistent with grade III and IV HRP. Therefore, the calculated sensitivity of a retinal examination in patients with hypertensive encephalopathy was 68%. The lack of retinal changes in hypertensive emergencies has been reported previously yet to our knowledge never been quantified.8,9
A possible explanation for the lack of retinal abnormalities could lie in the scarce sympathetic innervation of arteries supplying the posterior region of the brain, which is predominantly affected in hypertensive encephalopathy, compared to arteries originating from the middle cerebral artery that supply the retina. The posterior cerebral artery is subject to a lower damping of blood pressure oscillations compared to flow in the middle cerebral artery, which may be therefore more protected from hyperperfusion at high blood pressure values. In our study, patients with hypertensive encephalopathy and grade III or IV HRP were on average 13 years older and had higher systolic and diastolic BP values at admission. A likely explanation for these differences could be that these older patients were longer exposed to chronic hypertension resulting in a better adaptation of cerebral autoregulation to higher BP values. Disruption of the blood-brain barrier and development of cerebral edema therefore occurred at higher BP values in these patients compared to younger patients without retinal abnormalities. As a result of the chronic exposure to high BP levels, patients with hypertensive encephalopathy may have experienced more hypertensive organ damage as evidenced by the presence of grade III and IV HRP. This is supported by the finding that these patients tended to have more left ventricular hypertrophy and higher serum creatinine levels. Due to the limited group size these latter differences did not reach significance. Apart from their younger age and lower BP values, patients presenting with hypertensive encephalopathy, but lacking HRP were more frequently black. This may raise the question whether HRP can be reliably assessed in black patients and whether the prevalence of HRP in black patients is lower than in white patients. A previous report on grading of HRP in patients suspected of having malignant hypertension using retinal photographs showed that flame shaped hemorrhages and cotton wool spots that are consistent with grade III HRP could be reliably assessed, but that observers were less likely to agree on the presence or absence of papilledema (grade IV HRP). However, papilledema as the only retinal abnormality is an infrequent finding in patients with malignant hypertension. Specific data on observer agreement according to ethnic background in patients suspected of having malignant hypertension are lacking, but population based studies have shown that flame shaped hemorrhages and cotton wool spots can be reliably assessed in multi-ethnic communities with weighted k coefficients of 0.97 and 0.95 respectively. Observer agreement with regard to the assessment of HRP, including grade I and II, is not different between black and white individuals. Several studies describe that pupillary dilation induced by different mydriatic agents is stronger in light than in dark irides. Therefore a proper evaluation of the optic fundi in black patients in this study may have been hampered. However, a combination of tropicamide and phenylephrine eye drops, used by ophthalmologists in our hospital, produces adequate pupillary dilation irrespective of iris pigmentation. With regard to the prevalence of HRP, a previous observational study in the 1960s suggested that HRP in patients with severe hypertension was less frequently observed in black compared
to white subjects. However, other studies performed in the same decade noted that HRP was more common in blacks compared to whites. A more recent large population-based study showed that HRP was more common in black than in white individuals, but that the increased prevalence of HRP could largely be explained by differences in BP values and severity of hypertension. Thus, it appears that HRP can be reliably assessed, also with direct funduscopy, and is not more difficult to detect or less prevalent in black than in white patients.

The explanation for our observation that black patients with hypertensive encephalopathy more often lacked HRP, may be associated with the aforementioned difference in age and degree of exposure to chronic hypertension. Hypertension in black patients is known to be more severe and to develop at a younger age compared to white subjects. A recent cross-sectional survey conducted in Amsterdam in 2005 showed that in the catchment area of our hospital black individuals with hypertension were younger and had higher blood pressure values compared to white subjects. It is likely, that cerebral autoregulation had less time to adapt to these higher BP values in these patients, resulting in the development of hypertensive encephalopathy at relatively low BP levels.

Finally, as hypertensive encephalopathy is a clinical diagnosis, differences in clinical characteristics between patients with and without grade III or IV HRP may arouse the suggestion that severe hypertension could have been an epiphenomenon of the neurological symptoms of hypertensive encephalopathy. However resolution of the complaints after BP control in all included patients and the absence of other explanations for the neurological symptoms strongly suggest a causal relation. Furthermore we identified in 196 consecutive patients admitted with severe hypertension, a similar percentage (17%) of patients with hypertensive encephalopathy as was earlier observed in Glasgow, which strengthens our confidence in the patient selection.

This study has some limitations. Firstly, in a retrospective study there is always a possibility of coding errors. To optimize inclusion of all patients with hypertensive encephalopathy, we carried out a sensitivity analysis which revealed that no patients were discharged fulfilling the clinical criteria of hypertensive encephalopathy. Secondly, for this analysis we have relied on the description of the retinal findings using direct funduscopy. Although data on the reproducibility in the assessment of grade III and IV HRP using direct funduscopy are lacking, a detailed description of the optic disc and accurate grading of cotton wool spots and hemorrhages in diabetic retinopathy are well reproducible with κ-values of 0.64 and 0.71 respectively. Furthermore, we believe that our reliance on the reporting of retinal abnormalities by various ophthalmologists and neurologists reflects daily practice where the ophthalmologist or neurologist on call will be approached to assess the presence of HRP at the emergency room. Thirdly, we excluded three patients with incomplete reports on retinal examination performed by neurologists, but chose not to exclusively report on
the fundoscopic assessment by ophthalmologists to avoid selection bias. Neurologists mainly focus on the optic nerve and did not routinely dilate pupils before performing a retinal examination. Therefore they may be less comprehensive in reporting other retinal abnormalities. Because neurologists were responsible for only a small number of retinal examinations we believe that their findings do not affect our conclusions. Finally, the positive predictive value could not be calculated because the number of patients who presented with severe hypertension, but had no retinal abnormalities or clinical characteristics suggestive of hypertensive encephalopathy could not be reliably determined.

Although funduscopy is useful in patients suspected of hypertensive encephalopathy to discriminate hypertensive urgencies from emergencies, one third of patients admitted with hypertensive encephalopathy lack retinal abnormalities consistent with grade III or IV HRP. Recognition of this condition could therefore be hampered in patients with subtle neurological symptoms. Therefore, admission should not rely on the presence of grade III or IV hypertensive retinopathy alone, but should also include a careful neurological examination.
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