ies and 50% basilar artery stenosis confirming the thrombotic nature of the stroke. No cardiac source of embolism was found. Therefore, given the initial evidence of right vertebral artery occlusion by magnetic resonance angiography, we suspect that the progression to bilateral involvement was due to occlusion of a penetrating branch, although unfortunately the autopsy report did not focus on the origins of the anterior spinal arteries and no cerebral angiogram was performed.

MMS accounted for less than 0.5% of all cerebral infarcts in one series [1] and a similar number was reported in a 700-autopsy report [7]. Up to 1996, only 40 well-documented cases were reported [6], and this condition still remains a diagnostic challenge because of the heterogeneous clinical presentations [6].

In our patient the presence of upbeat nystagmus was an important diagnostic clue. It is thought to be secondary to medial longitudinal fasciculus involvement, although others proposed the involvement of the nucleus intercalatus of Starderini [8]. However, previous reports understated the diagnostic importance of the upbeat nystagmus [1], including the largest case series of MMS published in 1995 and 2004 [9, 10] because of the heterogeneous clinical presentation of the MMS.

In summary, we present the first concomitant DWI and autopsy-documented case of progression of right to bilateral anteromedial medullary ischemia. It also points to the need of early suspicion of peritonitis or other abdominal infection in patients with bilateral brainstem ischemia and unexplained fever. Similar to patients with spinal cord injury, they may develop threatening abdominal infections without the classical signs of peritoneal irritation [11].

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Cerebral Hemodynamics and Autoregulation in Reversible Posterior Leukoencephalopathy Syndrome Caused by Pre-/Eclampsia

Eckard Oehm², Andreas Hetzel³, Thomas Els², Ansgar Berlis³, Christoph Keck³, Hans-Gerd Will², Matthias Reinhard¹
²Departments of ¹Neurology, ²Neuroradiology and ³Obstetrics and Gynecology, University of Freiburg, Freiburg, and ⁴Department of Neurology, Clinical Center Villingen-Schwenningen, Villingen-Schwenningen, Germany

Introduction

Eclampsia accounts for nearly 50% of ischemic strokes during pregnancy and puerperium [1]. ‘Pre-eclampsia’ is defined as hypertension with proteinuria, edema or both induced by pregnancy. Neurological manifestations range from diffuse vegetative signs to focal deficits like amaurosis and sensorimotor impairment. In case of additional seizures or coma, the condition is called ‘eclampsia’. Pre-/eclampsia is thought to arise from immunological changes during trophoblast invasion, leading to chronic placental ischemia and release of vasoactive cytokines and mediators.

The underlying cerebrovascular pathophysiology is still poorly understood. On computed tomography and magnetic resonance imaging (MRI), pre-/eclampsia presents with the typical morphological lesion pattern of ‘reversible posterior leukoencephalopathy syndrome’ (RPLS) which is characterized by a multifocal, often symmetrical, vasogenic brain edema, predominantly in the posterior portions of the cerebral white matter and cortex [2].

During severe pre-/eclampsia, transcranial Doppler sonography (TCD) showed increased blood flow velocities in the basal cerebral arteries [3–7]. It is unclear whether this indicates cerebral hyperperfusion, vasospasm or both. Single-photon emission computed tomography revealed focal hyperperfusion [8], while angiographic studies reported intracranial vasospasms [9, 10].

Although cerebral dysautoregulation is thought to be of major influence on the development of RPLS and eclamptic encephalopathy, it has rarely been confirmed by autoregulation testing. We thus studied cerebral hemodynamics and autoregulation in 4 consecutive patients with pre-/eclampsia.

Case Descriptions

Patients and Methods. Between August 2001 and April 2003, four healthy primiparous women with normal pregnancy and puerperium until onset of pre-/eclampsia were admitted to our intensive-care unit. Severe pre-/eclampsia was defined as diastolic blood pressure > 90 mm Hg or systolic blood pressure > 140 mm Hg with proteinuria >0.3 g/l in a 24-hour collection, edema or both. As a control group for assessment of cerebral autoregulation, 8 age-matched healthy nonpregnant women and 5 healthy pregnant women (week of gestation 34–37) were studied. Extracranial duplex sonography was carried out using standard equipment (HD1 3500, ATL, USA). TCD measurements were performed with a Multi Dop x4 using a 2-MHz probe (DWL, Sipplingen, Germany) in all basal cerebral arteries. The resistance index (RI) was calculated from the waveform of cerebral blood flow velocity (CBFV) by the formula RI = (CBFV systolic – CBFV diastolic)/CBFV systolic. Dynamic
cerebral autoregulation (DCA) was assessed using transfer function analysis and the deep breathing method, yielding the phase shift and gain between arterial blood pressure (ABP) and CBFV oscillations at 0.1 Hz as surrogate markers for autoregulatory ability (for a detailed description, see elsewhere [11]). CBFV was monitored in both middle cerebral arteries by TCD. ABP was recorded continuously via finger plethysmography (Finapres). MRI and two-dimensional time-of-flight magnetic resonance angiography (MRA) were performed on a Siemens Vision 1.5 T with standard head coil (Siemens AG, Erlangen, Germany).

Clinical Course. Patient characteristics are given in table 1. For anticonvulsive treatment, magnesium sulfate was applied intravenously in all patients; valproate was added in patient 3, metoprolol and temporarily urapidil (not before/during autoregulatory measurements) in patient 4. Neurological symptoms resolved completely in all patients within 2–3 days.

MRI Results. Cortical, subcortical and deep white matter lesions predominantly in the occipital and parietal lobes were found in all patients (fig. 1a). Less frequently the edema was detected in the temporal lobes, basal ganglia, pons and cerebellum. Venous and

Fig. 1. a Initial fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted (DWI) scans revealing cortical, subcortical and basal ganglial lesions. b Follow-up investigations between days 3 and 7 demonstrating widely resolved cerebral edema in patient 3 and 4. Patient 1 showed only partial recovery, probably due to the short interval between scans. No follow-up scans were performed in patient 2.
arterial time-of-flight MRA showed normal findings without evidence of venous thrombosis or vasospasms in patients 1–3, while patient 4 showed diffuse vasoconstrictions of all basal cerebral arteries, especially both A1 segments and the left M1 segment on day 2 (small arrows) and improved signal of all intracranial vessels due to increased flow on day 7. Large arrows indicate reduction in vessel diameter in both distal internal carotid arteries on days 2 and 7.

**Fig. 2.** Time-of-flight MRA on days 2 and 7 after eclampsia onset in patient 4. It shows diffuse vasoconstrictions of all basal cerebral arteries, especially both A1 segments and the left M1 segment on day 2 (small arrows) and improved signal of all intracranial vessels due to increased flow on day 7. Large arrows indicate reduction in vessel diameter in both distal internal carotid arteries.

**Table 1.** Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>Clinical onset (days after delivery)</th>
<th>ABP on admission (mm Hg)</th>
<th>Proteinuria (mg/l/24 h)</th>
<th>Edema</th>
<th>Neurological symptoms in chronological order</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>eclampsia</td>
<td>6</td>
<td>145/95</td>
<td>110</td>
<td>–</td>
<td>series of 7 grand mal seizures</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>severe pre-eclampsia</td>
<td>2</td>
<td>180/110</td>
<td>300</td>
<td>–</td>
<td>complete bihemispheric cortical amaurosis</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>eclampsia</td>
<td>6</td>
<td>170/105</td>
<td>110</td>
<td>+</td>
<td>headache, vertigo, reduced consciousness, impaired orientation, bilateral cortical amaurosis, single grand mal seizure</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>eclampsia, HELLP syndrome</td>
<td>0</td>
<td>180/100</td>
<td>410</td>
<td>–</td>
<td>2 grand mal seizures, blurred vision</td>
</tr>
</tbody>
</table>

**Discussion**

In pre-/eclampsia, most authors presume a severe rise in ABP, exceeding the capacity of cerebral autoregulation, followed by pressure-passive dilation of the resistance vessels, cerebral hyperperfusion, blood-brain barrier damage, fluid and protein leakage, resulting in brain edema and petechial hemorrhage [2, 12–14].

RPLS is a descriptive definition for the resulting transient brain edema predominantly in the parieto-occipital region. A limitation of the present series might be that autoregulation was measured only in the more easily accessible middle cerebral artery. However, although RPLS seems to be focally enhanced in the posterior circulation presumably due to a reduced sympathetic innervation of the vertebrobasilar vessels [2, 8, 15], it is a generalized disease with affection of the whole cerebral macro- and microperfusion. This is supported by our results, demonstrating involvement of all basal cerebral arteries by TCD and ubiquitous capillary leakage presenting as reversible vasogenic edema on MRI. We thus assume that the severe impairment of autoregulation dynamics in eclampsia showed in the middle cerebral artery would also have been observed in the posterior cerebral artery.

Physiologically, cerebral autoregulation keeps cerebral blood flow constant within a wide range of mean systemic blood pressure and not until a rise above 150 mm Hg when the autoregulatory...
mechanism fails, resulting in the cascade described above [16]. In agreement with other studies none of our patients had a mean systemic blood pressure exceeding 125 mm Hg [2, 17, 18]. Nevertheless, as shown by the markedly increased CBFV, there seems to be a 'breakthrough' pointing to disturbance of the protective cerebral autoregulatory mechanism. Recently, Cipolla et al. [19] have shown that pressure-induced myogenic activity is diminished in the posterior cerebral artery of rats during late pregnancy and postpartum. Their results suggest that cerebral circulation is predisposed to forced dilation at lower pressures and secondary hyperperfusion when blood pressure is elevated, as occurs during eclampsia. Mean CBFV usually decreases significantly during normal gestation [20]. However, in case of pre-/eclampsia, it increases up to 100% correlating significantly with clinical severity [3, 5]. Surpris-

Table 2. Course of cerebral and systemic hemodynamic parameters

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Day</th>
<th>CBFV, cm/s</th>
<th>Resistance index</th>
<th>MAP mm Hg</th>
<th>HR beats/min</th>
<th>Hct %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>143/43</td>
<td>0.50/0.50</td>
<td>102</td>
<td>75</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>35/35</td>
<td>0.78/0.78</td>
<td>103</td>
<td>105</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>50/50</td>
<td>0.25/0.25</td>
<td>87</td>
<td>88</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>103/112</td>
<td>0.49/0.45</td>
<td>97</td>
<td>88</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>77/103</td>
<td>0.53/0.47</td>
<td>97</td>
<td>88</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>81/98</td>
<td>0.58/0.49</td>
<td>96</td>
<td>88</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>73/91</td>
<td>0.40/0.44</td>
<td>90</td>
<td>90</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>91/80</td>
<td>0.44/0.56</td>
<td>113</td>
<td>55</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>76/75</td>
<td>0.50/0.49</td>
<td>107</td>
<td>80</td>
<td>33</td>
</tr>
<tr>
<td>10</td>
<td>89/69</td>
<td>67/72</td>
<td>0.57/0.50</td>
<td>88</td>
<td>75</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>48/60</td>
<td>0.60/0.60</td>
<td>117</td>
<td>87</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>68/70</td>
<td>0.30/0.29</td>
<td>113</td>
<td>106</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>160/140</td>
<td>0.30/0.39</td>
<td>123</td>
<td>105</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>128/113</td>
<td>0.60/0.60</td>
<td>92</td>
<td>96</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>125/140</td>
<td>0.37/0.39</td>
<td>115</td>
<td>108</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>107/91</td>
<td>0.50/0.44</td>
<td>80</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>77/67</td>
<td>0.53/0.54</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Note the severe temporary increase in heart-rate-adjusted mean CBFV in the middle (MCA) and posterior cerebral arteries (PCA). Concurrently, the RI decreased substantially. ICA = Internal carotid artery; ACA = anterior cerebral artery; R = right; L = left. For comparison, mean hemodynamic parameters of regular pregnancy on day 3 of the puerperium are [27]: CBFV = 74.2 cm/s (MCA), RI = 0.56 (MCA), mean arterial pressure (MAP) = 82.9 mm Hg, heart rate (HR) = 82.2 beats/min, hematocrit (Hct) = 32%.

Table 3. Results for dynamic cerebral autoregulation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Day</th>
<th>Phase shift, degrees</th>
<th>Gain, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R MCA</td>
<td>L MCA</td>
<td>R MCA</td>
</tr>
<tr>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>11.5</td>
<td>9.2</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>10.1</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>–4.3</td>
<td>15.2</td>
</tr>
</tbody>
</table>

Nonpregnant controls (n = 8): 45.6 (21.6–59.3) 1.02 (0.50–1.25)

Pregnant controls (n = 5): 63.2 (43.5–93.7) 1.09 (0.85–1.19)

Transfer function analysis of respiratorily induced 0.1-Hz oscillations of CBFV and ABP. Phase shift and gain were determined at 0.1 Hz. For controls, data are given as medians, with ranges in parentheses. MCA = Middle cerebral artery; R = right; L = left.
ingly, our TCD findings during the first 2 days were nearly normal, although clinical symptoms and MRI lesions were worst at this time. Subsequently, clinical symptoms and parenchymal lesions resolved, whilst TCD values showed major alteration. This was probably favored by increased ABP, lowered hematocrit and reduced vessel resistance. Although this phenomenon was already reported by other authors, a distinct explanation is still missing [21–23]. In patient 4 the CBFV increase might reflect generalized vasospasms of the basal arteries as confirmed by MRA, but in the other patients vasocostrictions were not observed pointing rather to the presence of hyperperfusion [24].

The hemodynamic parameters in the present series were obtained under medication with intravenous magnesium sulfate. This drug is discussed to have vasodilating properties that might reduce cerebral arteriolar resistance [25]. It has, however, been demonstrated that the eclamptic changes in CBFV remain constant after discontinuing magnesium sulfate [6]. We thus assume that our results are not severely influenced by this drug effect.

We found dynamic cerebral autoregulation to be early and severely impaired in pre-/eclampsia. The observed phase shift reduction might therefore be a sensitive and early parameter for cerebral hemodynamic disturbance in pre-/eclampsia. The gain of the transfer function between ABP and CBFV oscillations represents the extent to which the transfer of dynamic ABP oscillations onto CBFV is damped. Impairment of cerebral autoregulation might lead to reduced damping and thus higher gain. Interestingly, a recent study found a higher gain in the posterior circulation as compared with the middle cerebral artery, hypothesizing a higher vulnerability to amplitude changes of ABP [26]. The elevated gain in our patients points to a decreased damping of blood pressure oscillations probably contributing to the ‘breakthrough’ mechanism leading to eclamptic edema.

In conclusion, we have demonstrated that cerebral hemodynamics and DCA are severely impaired in pre-/eclampsia. Decreased phase shift seems to be an early and sensitive parameter in the diagnosis of disturbed cerebral hemodynamics in pre-/eclampsia patients. Further investigations have to prove whether assessment of cerebral hemodynamics and DCA in high-risk pregnancies can be used as predictors for the development of pre-/eclampsia.

References

Matthias Reinhard, MD
Neurologische Universitätsklinik, Universität Freiburg
Breisacher Strasse 64
DE-79106 Freiburg (Germany)
Tel. +49 761 270 5001, Fax +49 7664 270 5390
E-Mail reinhard@nu.ukl.uni-freiburg.de