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

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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 symmetric, 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 (HDI 3500, ATL, USA). TCD measurements were performed with a Multi Dop $\times 4$ 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

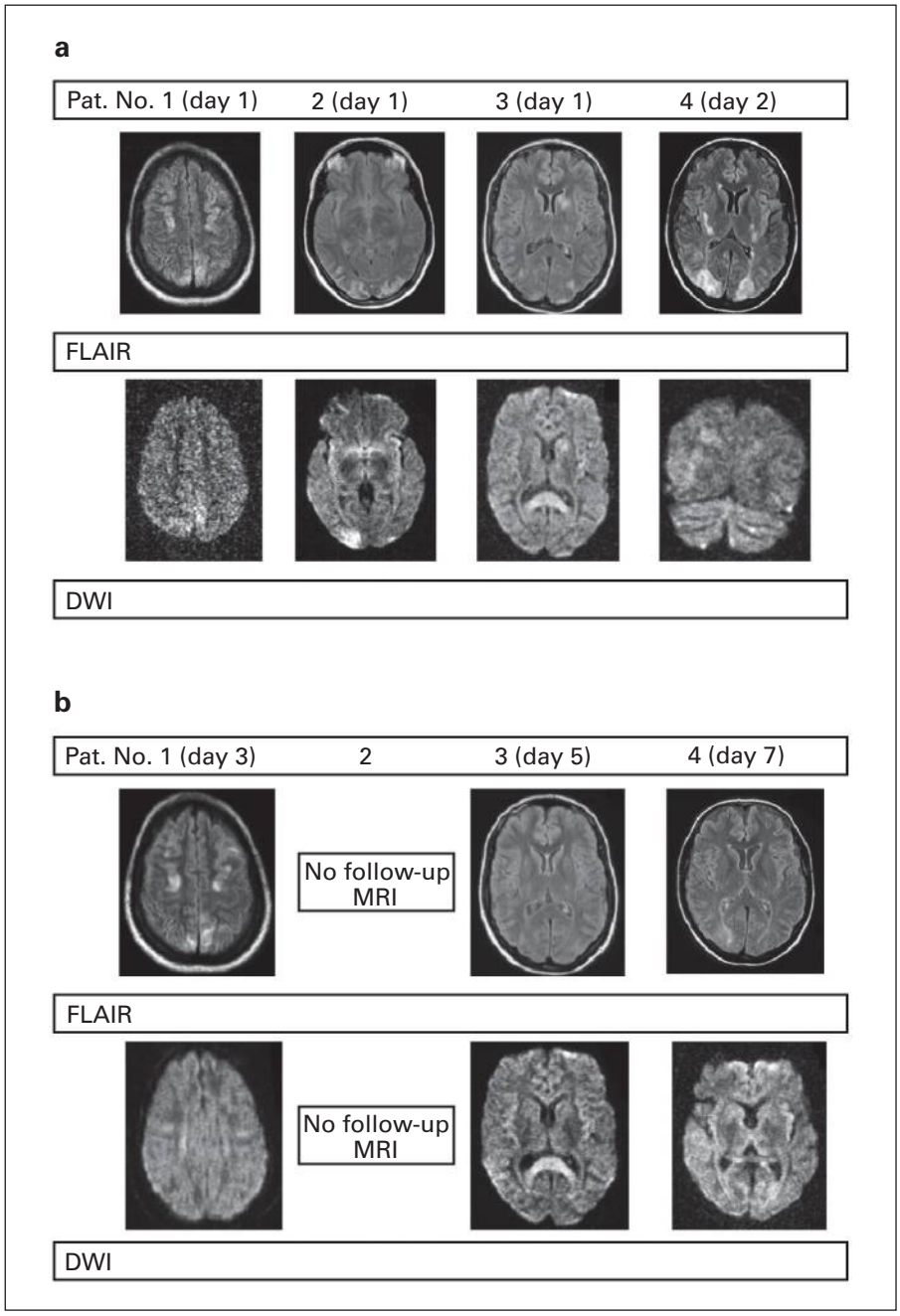

Fig. 1. a Initial fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted (DWI) scans revealing cortical, subcortical and basal ganglial lesions. **b** Follow-up investigations between days 3 and 7 demonstrating widely resolved cerebral edema in patient 3 and 4. Patient 1 showed only partial recovery, probably due to the short interval between scans. No follow-up scans were performed in patient 2.

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

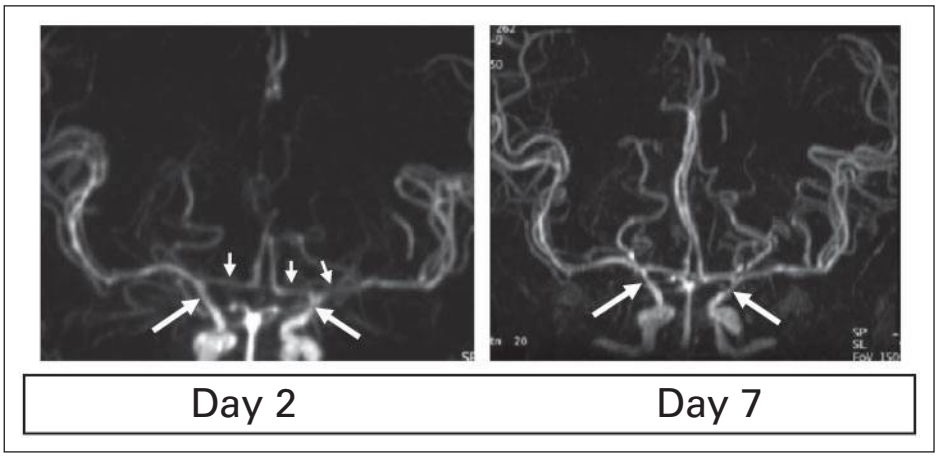

Fig. 2. Time-of-flight MRA on days 2 and 7 after eclampsia onset in patient 4. It shows diffuse vasoconstrictions of all basal cerebral arteries, especially both A1 segments and the left M1 segment on day 2 (small arrows) and improved signal of all intracranial vessels due to increased flow on day 7.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

Table 1. Patient characteristics

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

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 arteries (fig. 2). The MRI changes improved markedly within 5–6 days (patients 3, 4), but sustained vasospams were still present in patient 4 at control on day 7 (fig. 1b).

Course of Cerebral and Systemic Hemodynamics. CBFV was increased in all major cerebral arteries with a maximum on days 2–5 after disease onset (table 2). Patient 1 did not show increased CBFV, but data acquisition was limited to the first day of eclampsia onset. Mean ABP remained constant (patient 2) or increased slightly (patients 3,4), while the hematocrit decreased (patients 2–4) due to hemodilution.

Cerebral Autoregulation. Because of movement artifacts accurate data recording analysis was not possible in patient 1. Compared with healthy pregnant and nonpregnant controls, phase shift was reduced and transfer function gain was elevated at least on one side in all patients (table 3). Compared to the other cerebral hemodynamic data, DCA parameters presented with two interesting aspects: (1) phase shift was reduced in all patients beginning on the first day of pre-/eclampsia manifestation; (2) phase shift could be already reduced, although hemodynamic standard parameters (CBFV and RI) were still within the normal range (patient 2).

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

Table 2. Course of cerebral and systemic hemodynamic parameters

Patient No.	Day	CBFV, cm/s				Resistance index				MAP mm Hg	HR beats/min	Hct %
		R/L ICA	R/L ACA	R/L MCA	R/L PCA	R/L ICA	R/L ACA	R/L MCA	R/L PCA			
1	1	143/43	61/53	61/61	41/45	0.50/0.50	0.45/0.50	0.45/0.45	0.47/0.56	102	75	41
2	2	35/35	45/43	68/53	51/39	0.78/0.78	0.56/0.50	0.48/0.50	0.44/0.53	103	105	36
	3	–	50/50	115/83	50/47	–	0.25/0.25	0.45/0.36	0.43/0.33	87	88	39
	5	–	103/112	125/119	95/95	–	0.49/0.45	0.43/0.45	0.40/0.40	97	88	41
	7	–	77/103	85/100	33/35	–	0.53/0.47	0.52/0.54	0.59/0.50	97	88	37
	9	–	81/98	79/90	36/39	–	0.58/0.49	0.58/0.52	0.60/0.55	96	88	–
3	3	73/91	107/107	133/133	51/33	0.40/0.44	0.50/0.50	0.50/0.50	0.44/0.67	90	90	35
	5	91/80	107/119	165/165	53/73	0.44/0.56	0.50/0.51	0.47/0.47	0.50/0.40	113	55	30
	7	75/95	107/107	141/141	37/32	0.50/0.49	0.50/0.50	0.44/0.44	0.33/0.50	107	80	33
	10	69/69	67/72	101/101	47/47	0.57/0.57	0.67/0.60	0.55/0.55	0.33/0.33	88	75	34
4	1	48/60	113/101	133/133	80/93	0.60/0.60	0.56/0.55	0.50/0.50	0.50/0.63	117	87	24
	2	68/70	140/146	235/240	170/–	0.30/0.29	0.44/0.38	0.38/0.40	0.30/–	113	106	24
	4	–	160/140	236/240	110/100	–	0.40/0.44	0.38/0.40	0.43/0.44	123	105	28
	5	48/48	128/113	217/200	100/96	0.60/0.60	0.30/0.56	0.38/0.43	0.43/0.38	92	96	26
	6	88/90	125/140	190/180	140/110	0.37/0.39	0.53/0.44	0.48/0.50	0.44/0.43	115	108	27
	8	–	107/91	160/148	61/75	–	0.50/0.44	0.50/0.49	0.45/0.50	–	80	–
	14	77/67	77/64	107/107	64/75	0.53/0.54	0.53/0.50	0.50/0.50	0.50/0.50	–	–	–

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

Patient	Day	Phase shift, degrees		Gain, %	
		R MCA	L MCA	R MCA	L MCA
1	–	–	–	–	–
2	2	11.5	9.2	1.25	1.39
3	5	10.1	–	1.27	–
4	1	–4.3	15.2	0.90	1.31
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.

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-

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 vasoconstrictions 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-/eclamptic 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.

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