

Cerebral haemodynamic pathologies in HELLP syndrome

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Abstract

The syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP syndrome) is understood as a unique variant of severe preeclampsia. This disorder complicates between 2 and 7% of gestations and is associated with a high perinatal morbidity and a maternal morbidity ranging between 1 and 4%. Intracerebral complications only rarely occur, especially intracerebral haemorrhage was described only in single cases, often correlated with fatal maternal outcome. The analysis of patients with HELLP syndrome treated at our hospital revealed three cases with severe neurological deterioration. Possible pathogenetic factors are discussed.

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1. Introduction

The syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP syndrome) is a severe complication in late pregnancy. It is mainly characterized by increased liver enzymes, a low platelet count and haemolysis. As defined by Weinstein in 1982 it is a separate disease, but may occur in pregnancy with a severe course of preeclampsia/eclampsia [1]. It increases perinatal and maternal morbidity and mortality [2,3]. According to the primary organ involvement, acute renal failure, abdominal complaints, and acute respiratory distress syndrome may occur. An underestimated phenomenon in HELLP syndrome are intracranial complications, which considerably contribute to maternal morbidity and mortality. We describe three cases of HELLP syndrome with serious neurological impairment documented by extensive neuroradiological examinations.

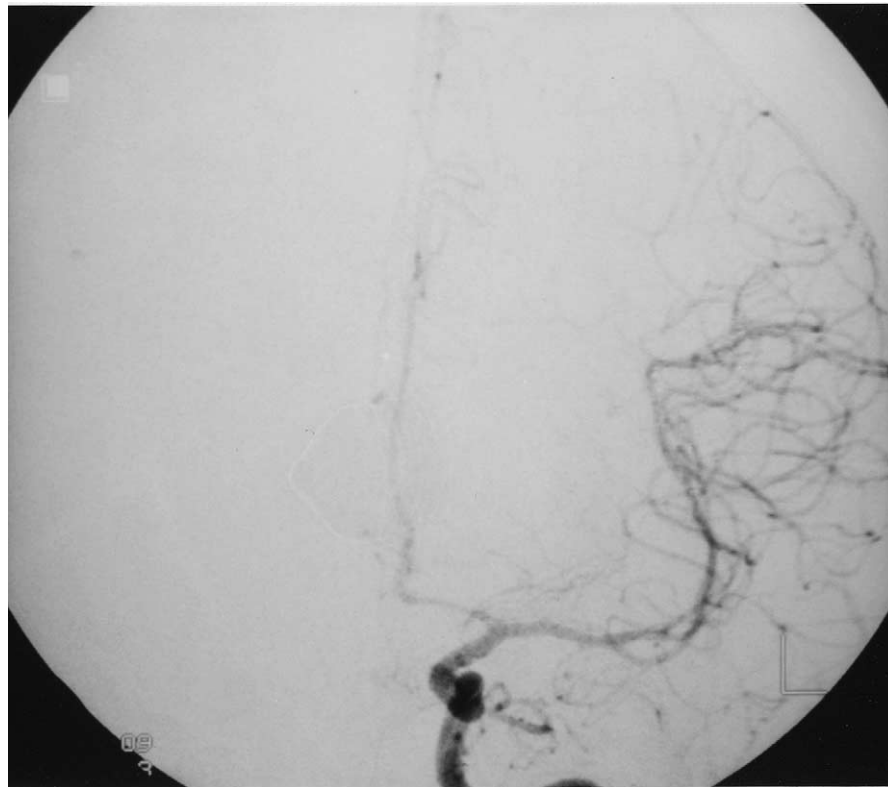
2. Case reports

2.1. Case 1

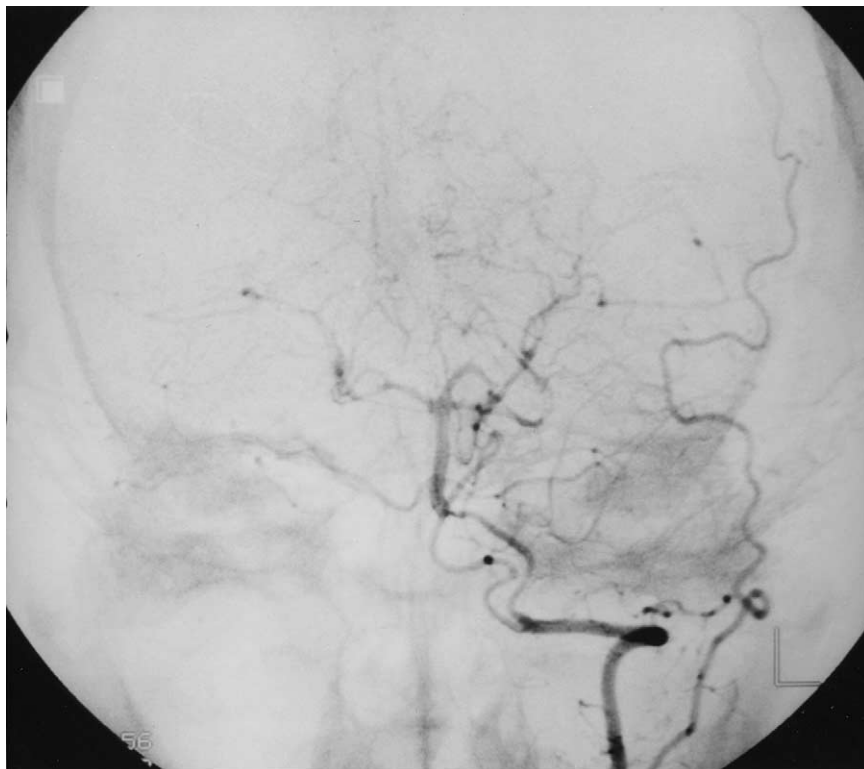
A 34-year-old primigrava (gemini after IVF and ICSI) presented at the 31st week. Based on clinical and laboratory assessment, the diagnosis of preeclampsia and HELLP syndrome was made. Caesarian section was performed under general anesthesia. The course of anesthesia and surgery was uneventful. She delivered two female infants both of 1700 g. During the first 24 h postpartum she developed progressive visual disturbances and binocular reduction of vision (<0.1) as well as optical ataxia. The further neurological examination revealed no abnormalities. CT scan and cerebral angiography were performed on the second day postpartum. In the CT scan multiple ischemic lesions of the basal ganglia, the bilateral parieto-occipital region and the cerebellar hemispheres were demonstrated. Transcranial Doppler sonography showed generalized vasospasm (Fig. 1a, b). These findings were confirmed by cerebral panangiography. After conservative treatment the patient recovered very well. No further visual disturbances or neurological symptoms appeared.

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(a)



(b)

Fig. 1. (a) Angiography of the left internal carotid artery showing vasospasm in the cerebral anterior artery, anteroposterior view. (b) Angiography of the left vertebral artery with vasospasm in the vertebral artery and the posterior cerebral artery, anteroposterior view.

2.2. Case 2

A 36-year-old woman, gravida IV (GIV), para II (PII) was admitted to the hospital due to acute severe epigastric pain at a gestational age of 39 weeks 6 days. Blood pressure on admittance was 150/100 mmHg. Antihypertensive therapy was performed. Haematologic analysis revealed thrombocytopenia of 91 000 per mm^3 platelets, while Hb was normal with 12.8 g/dl. Liver enzymes were markedly elevated with GOT of 799 U/l, GPT of 412 U/l and HBDH of 792 U/l. Due to a decrease in platelet count to 16 000 per mm^3 and drop of Hb to 10.6 g/dl as well as an increase of total bilirubin to 1.4 mg/dl and lactic dehydrogenase to 712 U/l a Caesarian section was initiated. At this time, the patient had macrohaematuria. However, she was well orientated and responded adequately. After thrombocyte substitution in order to minimize the risk of spontaneous haemorrhage an uneventful Caesarian section was performed. The patient was transferred to the intensive care unit afterwards. Weaning was started, but the patient remained comatose. Emergency CT scan revealed a large left-occipital intracerebral and intraventricular haemorrhage with consecutive hydrocephalus, cerebral oedema and midline-shift of 1.5 cm (Fig. 2).



Fig. 2. CT scan revealed a large left-occipital intracerebral and intraventricular haemorrhage with consecutive hydrocephalus, cerebral oedema and midline-shift of 1.5 cm.

Craniotomy was performed, the haematoma was evacuated and an ICP probe was placed. After the operation first of all the neurologic situation improved. The patient regained awareness. A repeat CT scan on the fourth day postpartum demonstrated a subtotal removal of the haematoma and reduced brain oedema. On the 11th day postpartum her neurological condition subacutely deteriorated again with development of unconsciousness. The CT scan at this time demonstrated several areas of low density in left frontal lobe, basal ganglia, and right parieto-occipital region (Fig. 3). Cerebral four-vessel-angiography showed diffuse massive vasospasm, which was narrowing all intracranial arteries (Fig. 4). There was no evidence of atherothrombosis, aneurysm or vascular malformation. Flow velocity measurements using a Doppler ultrasound probe confirmed the suspected vasospasm on both sides.

The further course was fatal. The patient died in the state of cerebral death 3 weeks post partum.

2.3. Case 3

A 21-year old primigrava presented at 33rd week after sudden onset of a grand mal convulsion. She had reported upper abdominal pain a few days before

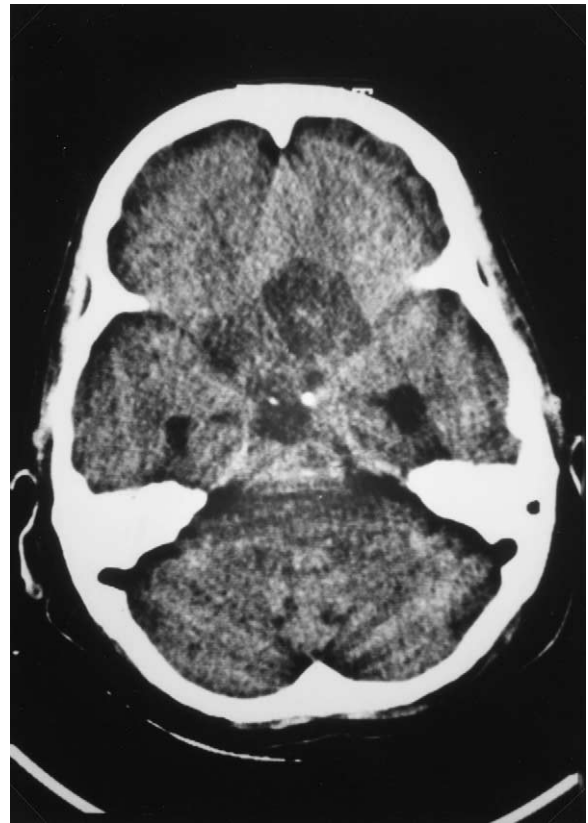


Fig. 3. CT scan demonstrated several areas of low density in both frontal lobes. Further scans showed hypodensities in bilateral basal ganglia and both parieto-occipital regions.

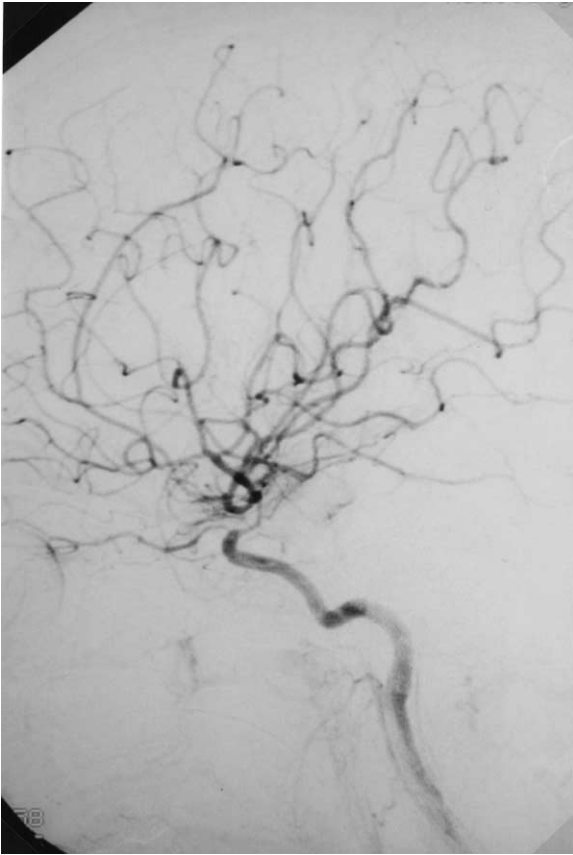


Fig. 4. Angiography of the right internal carotid artery showing massive vasospasm, lateral view.

admittance. Neither headache nor visual disturbances occurred. Based on clinical and laboratory assessment, the diagnosis of preeclampsia with HELLP syndrome was made (hypertension, thrombocytes 34 per nl, GOT 159 U/l, GPT 103 U/l). An urgent Caesarian section was performed. Postoperatively, a generalized epileptic state occurred. CT scan demonstrated hypodensities in both parietal regions. Neurological examination revealed slight left hemiparesis and a mild organic mental syndrome. MRI showed extensive leukencephalopathic lesions in both frontal, parietal, and posterior subcortical regions (Fig. 5). Almost all of these lesions proved to be completely reversible on a follow-up MRI on day 8 after delivery. The following course was uneventful, neurological symptoms did not persist. The laboratory parameters normalized.

3. Discussion

The HELLP-syndrome is a symptom-complex attributed to a subgroup of patients with preeclampsia, who

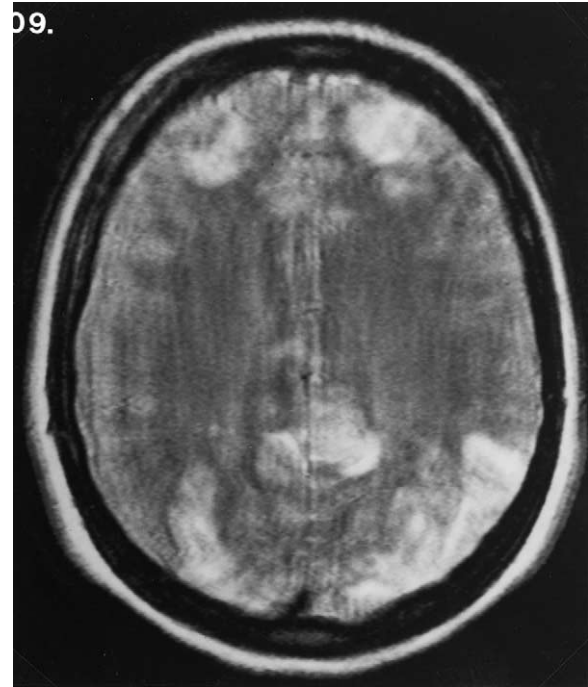


Fig. 5. MRI on the day of admission showed extensive leukencephalopathic lesions in both frontal, parietal, and posterior subcortical regions.

develop haemolysis, high liver enzyme levels and low platelet counts known as a serious and life-threatening disease. The associated perinatal and maternal morbidity is well recognized. Acute renal failure, liver haematoma, disseminated intravascular coagulation, and abruptio placentae due to disturbed blood coagulation are typical clinical findings leading to a maternal mortality rate ranging from 1 to 4% [4,5].

On the other side, cerebral manifestations of HELLP syndrome are rare. Severe complications including sinus thrombosis, eclamptic convulsions, brain oedema, acute cortical blindness, and intraparenchymal haemorrhage have been described in single cases [6–10]. Brain stem involvement is exceptionally associated with HELLP syndrome with a variable prognosis [11,12]. Only four cases of brain oedema were described in a prospective study by Sibai et al. including 442 pregnancies complicated by HELLP syndrome [4]. In contrast, Isler et al. found 45% cerebral haemorrhages when they analyzed the factors contributing to death in 54 women with HELLP syndrome; in 16% hypoxic ischemic encephalopathy caused an increased mortality risk [13].

Disturbances in cerebral haemodynamics have been accused to cause several neurological symptoms in cases of eclampsia/preeclampsia. Previous studies using the non-invasive transcranial Doppler technique reported haemodynamic changes like cerebral vasospasm to be

associated with HELLP syndrome [14,15]. Cerebral blood flow velocity was significantly higher in preeclamptic than in normotensive women and rose significantly in the postpartum period [16]. It has been suggested that this vasoconstrictive disorder associated with the preeclampsia/eclampsia syndrome is related to increased concentrations of haemoglobin derived from haemolysis [17]. Even in cases of HELLP syndrome, the haemolysis possibly leads to a release of considerable amounts of oxyhaemoglobin, which is the supposed cause of cerebral vasospasm [18–20]. A correlation of oxyhaemoglobin release and cerebral vasospasm due to oxyhaemoglobin-induced smooth muscle contraction was also found in patients with subarachnoid haemorrhage [19]. Due to the increased haemolysis in HELLP syndrome—in comparison to patients with preeclampsia/eclampsia—an increased rate of vasospasm was suspected, but could not be confirmed by Williams and Wilson, who did not find increased blood flow velocity as indicative for vasospasm in patients with HELLP syndrome [21].

Another main pathophysiological explanation regarding the pathogenesis of neurological disturbances is damage of the blood–brain-barrier usually associated with a break-down of cerebral autoregulation and subsequent hyperperfusion [22]. Zunker et al. compared maternal cerebral haemodynamics, as assessed by transcranial Doppler, with clinical and radiological findings in different types of pregnancy-related hypertension [23]. Endothelial dysfunction and the breakdown of cerebral autoregulation with consecutive hyperperfusion and vasogenic oedema were suspected to cause the neurological deficits. It was suggested, that forced vasodilatation, probably due to passive overdistension of cerebral arterioles rather than vasospasm, was responsible for the observed high flow velocities [24]. Whereas highest mean velocity values were measured in patients with eclampsia/preeclampsia syndrome, only mild or no changes were registered in HELLP syndrome. Neurological deficits in patients with HELLP syndrome were also suspected to be related to hepatic and renal failure [25] rather than to altered cerebral haemodynamics. This may apply to single cases.

We are able to present a series of three cases with cerebral complications in HELLP-syndrome caused by either disturbances in cerebral autoregulation or cerebral vasospasm. No severe abnormalities in hepatic or renal function were observed, which could have led to renal or hepatic encephalopathy. Cerebral vasospasm was clearly documented in the first two cases by angiography, a third case of hyperperfusion and vasogenic oedema was shown by MRI. Therefore, in each case of neurological deterioration in HELLP-syndrome extensive neuroradiological examination needs to be performed. If necessary, haemodynamic and spasmolytic therapy should start immediately.

References

- [1] Weinstein L. Syndrome of hemolysis, elevated liver enzymes, and low platelet count: a severe consequence of hypertension in pregnancy. *Am J Obstet Gynecol* 1982;142:159–67.
- [2] Sibai BM, Taslimi MM, El-Nazer A, Amon E, Mabie BC, Ryan GM. Maternal-perinatal outcome associated with the syndrome of hemolysis, elevated liver enzymes, and low platelets in severe preeclampsia-eclampsia. *Am J Obstet Gynecol* 1986;155:501–509.
- [3] Martin JN, Jr, Blake PG, Perry KG, Jr, McCaul JF, Hess LW, Martin RW. The natural history of HELLP syndrome: patterns of disease progression and regression. *Am J Obstet Gynecol* 1991;164:1500–13.
- [4] Sibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Friedman SA. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). *Am J Obstet Gynecol* 1993;169:1000–6.
- [5] D'Anna R. HELLP syndrome. Remarks about pathogenesis and treatment. *Minerva Ginecol* 1996;48:147–54.
- [6] Friedmann W, Vogel M, Unger M, Martius G. Letaler Verlauf eines HELLP-syndroms. *Zentralbl Gynäkol* 1990;112:925–9.
- [7] Helguera-Martinez AM, Tenorio-Maranon R, Vigil-de Gracia PE, Garcia-Caceres E. HELLP syndrome. Analysis of 102 cases. *Ginecol Obstet Mex* 1996;64:528–33.
- [8] Tanner B, Ohler WG, Hawighorst S, Schaffer U, Knapstein PG. Complications in HELLP syndrome due to periparturient hemostatic disorder. *Zentralbl Gynäkol* 1996;118:213–20.
- [9] Crosby ET, Preston R. Obstetrical anesthesia for a parturient with preeclampsia, HELLP syndrome and acute cortical blindness. *Can J Anaesth* 1998;45:452–9.
- [10] Ebert AD, Hopp HS, Entezami M, Runkel S, Weitzel HK. Acute onset of blindness during labor: report of a case of transient cortical blindness in association with HELLP syndrome. *Eur J Obstet Gynecol Reprod Biol* 1999;84:111–3.
- [11] Imaizumi H, Nara S, Kaneko M, Chiba S, Tamakawa M. Magnetic resonance evaluation of brainstem dysfunction in eclampsia and the HELLP syndrome. *J Emerg Med* 1995;13:191–4.
- [12] Gutierrez-Garcia JM, Carreres A. Brain stem involvement in eclampsia and HELLP syndrome. *Rev Neurol* 1999;28:1162–6.
- [13] Isler CM, Rinehart BK, Terrone DA, Martin RW, Magann EF, Martin JN. Maternal mortality associated with HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. *Am J Obstet Gynecol* 1999;181:924–8.
- [14] Belfort MA, Saade GR. Retinal vasospasm associated with visual disturbance in preeclampsia: color flow Doppler findings. *Am J Obstet Gynecol* 1993;169:523–5.
- [15] Williams KP, MacLean C. Maternal cerebral vasospasm in eclampsia assessed by transcranial Doppler. *Am J Perinatol* 1993;10:143–244.
- [16] Köller H, Somville T, Aulich A, Seitz RJ. Reversible multifokale Enzephalopathie bei fulminanter Eklampsie. *Nervenarzt* 2001;72:312–6.
- [17] Sarrel PM, Lindsay DC, Poole-Wilson PA, Collins P. Hypothesis inhibition of endothelium derived relaxing factor by hemoglobin in the pathogenesis of preeclampsia. *Lancet* 1990;336:1030–2.
- [18] Woolfson RG, Williams DJ. Free hemoglobin and preeclampsia. *Lancet* 1990;336:1504.
- [19] MacDonald RL, Weir BKA. A review of hemoglobin and the pathogenesis of cerebral vasospasm. *Stroke* 1991;22:971–82.
- [20] Kobayashi T, Tokunaga N, Isoda H, Kanayama N, Terao T. Vasospasms are characteristic in cases with eclampsia/preeclampsia and HELLP syndrome: proposal of an angiospastic syndrome of pregnancy. *Semin Thromb Hemost* 2001;27:131–5.

- [21] Williams KP, Wilson S. Maternal middle cerebral artery velocity changes in HELLP syndrome versus pre-eclampsia. *Ultrasound Obstet Gynecol* 1998;11:195–8.
- [22] Lassen NA, Agnoli A. The upper limit of cerebral autoregulation of cerebral blood flow—on the pathogenesis of hypertensive encephalopathy. *Scand J Clin Lab Invest* 1973;30:113–6.
- [23] Zunker P, Happe S, Georgiadis AL, Louwen F, Georgiadis D, Ringelstein EB, Holzgreve W. Maternal cerebral hemodynamics in pregnancy-related hypertension. A prospective transcranial Doppler study. *Ultrasound Obstet Gynecol* 2000;16:179–87.
- [24] Zunker P, Ley-Pozo J, Louwen F, Schuierer G, Holzgreve W, Ringelstein EB. Cerebral hemodynamics in pre-eclampsia/eclampsia syndrome. *Ultrasound Obstet Gynecol* 1995;6:411–5.
- [25] Selcuk NY, Odabas AR, Cetinkaya R, Tonbul HZ, San A. Outcome of pregnancies with HELLP syndrome complicated by acute renal failure (1989–1999). *Renal Fail* 2000;22:319–27.