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DOI: [10.1159/000335826](https://doi.org/10.1159/000335826)**An Increased Pulsatility Index in Transcranial Doppler Sonography Is Associated with Shiga-Toxin-Related Encephalopathy in Hemolytic Uremic Syndrome**J.M. Albers^a, H. Pavenstaedt^b, C. Dlugos^b, P. Lebiedz^c,
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Shiga-toxin (Stx)-producing *Escherichia coli* (STEC) causes hemorrhagic diarrhea and the potentially lethal hemolytic uremic syndrome (HUS) in severe cases. In 20–50% of the patients, HUS is complicated by involvement of the central nervous system (HUS-N) [1, 2]. Common neurological symptoms are seizures, alteration of consciousness, focal neurological deficits, visual disturbances and brainstem symptoms. Neurological manifestations are associated with increased morbidity and mortality.

Histopathology suggests that endothelial damage in small intracerebral arteries caused by Stx leads to leakage and breakdown of the blood-brain barrier [3, 4]. Two case reports of HUS-N presented pathological findings during transcranial Doppler sonography (TCD) [5, 6] suggesting hyperperfusion or vasospasm of the affected arteries. We performed TCD in patients with STEC infection when patients suffered from massive neurological deterioration and 6 days thereafter to investigate whether changes were congruent with hyperperfusion or increased peripheral resistance in patients with proven HUS and HUS-N caused by STEC infection.

Case Report

Nine patients were treated in our hospital because of severe HUS caused by an infection with STEC during the EHEC outbreak in northern Germany in May 2011 (table 1). Stx-2 toxin was found in every patient. Five patients experienced neurological deterioration during the course of the disease (HUS-N). Four of them needed mechanical ventilation due to coma and recurring seizures.

In patients with HUS-N, TCD showed only slightly increased blood flow velocities of basal brain arteries (table 1). However, the mean resistance index (RI) and in particular the mean pulsatility index (PI) were significantly increased in patients with HUS-N, compared to HUS patients without neurological symptoms (mean PI/RI 1.11/0.62 vs. PI/RI 0.72/0.48, $p < 0.001$, Mann Whitney U test; table 1). The abnormalities declined after 6 days, corresponding to clinical improvement (table 1).

Discussion

The slightly increased blood flow velocities in conjunction with a significantly elevated PI and RI in HUS-N support findings from autopsy and animal studies, suggesting an Stx-mediated apoptosis and necrosis of endothelial cells as the hallmark of a toxic vasculopathy [1–4]. Stx-induced endothelial damage leading to breakdown of the blood-brain barrier causes swelling of the capillary bed and therefore increases the peripheral arterial resistance [1–4]. This explains the alterations of PI and RI of patients with HUS-N.

The changes on TCD are specifically found in patients with neurological involvement compared to the normal findings in patients without neurological symptoms.

The TCD investigations have been performed after onset of neurological symptoms, which is a limitation of the study. Therefore, a prediction of the HUS-related neurological symptoms by TCD was not possible. However, the first TCD of patient 1 showed only small changes of blood flow velocity, PI and RI, while initial TCD measurements of patients 2–4 revealed more substantial changes. In accordance with these findings, patients 2–4 suffered from massive neurological symptoms (table 1), even in the 6-day follow-up, while patient 1 initially experienced mild neurological involvement. Six days thereafter, the neurological status of patient 1 had become normal. Thus, clinical symptoms and changes of the TCD were parallel to a large extent; however, our case number is too small to draw definite conclusions on this finding.

Conclusion

TCD in patients with STEC-induced encephalopathy showed significantly increased PI and RI reflecting the higher peripheral resistance in terminal vessels. TCD might be a noninvasive, early-to-apply diagnostic and monitoring tool to estimate the risk and prognosis of HUS-related neurological involvement.

Disclosure Statement

E.B. Ringelstein has received travel expenses and honoraria from Boehringer Ingelheim, Sygnis, Neurobiological Technolo-

M.A. Ritter and R. Ditttrich contributed equally to this work.

Table 1. Blood flow velocity (cm/s), PI and RI measured by TCD, clinical and MRI findings

Pa- tient	Sex	Age	CS r/PI/RI	CS l/PI/RI	MCA r/PI/RI	MCA l/PI/RI	ACA r/PI/RI	ACA l/PI/RI	PCA r/PI/RI	PCA l/RI/PI	Mean PI/RI	Neu- rology	MRI find- ings	Stx
HUS-N patients														
1	f	28	150/1/0.6	150/1/0.6	160/0.82/0.53	200/0.86/0.55	150/0.67/0.47	125/0.54/0.4	60/0.75/0.5	90/0.88/0.56	0.82/0.53	D, S, Sz	+	+
1'	f		125/0.79/0.52	150/0.79/0.5	175/0.71/0.49	180/0.88/0.56	130/0.84/0.54	130/0.84/0.54	75/0.67/0.47	100/0.75/0.5	0.81/0.52	normal	n.d.	+
2	f	68	125/1.7/0.8	n.a.	125/1.7/0.8	n.a.	110/1.41/0.72	70/1.36/0.71	60/1.88/0.83	60/1.2/0.67	1.54/0.76	C, Sz	-	+
2'	f		140/1.36/0.71	100/1.31/0.7	160/1.27/0.68	90/1.2/0.67	125/1/0.6	160/1.1/0.63	100/1.3/0.7	50/1.71/0.8	1.21/0.67	D, S	n.d.	+
3	f	39	130/0.84/0.54	100/1/0.6	150/1/0.6	100/1/0.6	125/1/0.6	90/1.2/0.66	75/1.2/0.67	75/1.2/0.67	1.01/0.6	C, Sz, DR	+	+
3'	f		140/0.92/0.57	75/1/0.6	140/0.92/0.57	150/1/0.6	100/1.3/0.7	110/0.85/0.55	75/1.2/0.67	50/1/0.6	0.99/0.6	D, S	n.d.	+
4	f	23	125/1/0.6	150/1/0.6	150/1.43/0.73	175/1.17/0.66	125/1/0.6	150/1.2/0.66	50/1/0.6	125/1/0.6	1.13/0.64	C, Sz, DR	+	+
4'	f		200/1.07/0.63	150/0.75/0.5	200/1.07/0.63	160/0.82/0.53	100/1/0.6	180/0.75/0.5	90/0.63/0.44	75/1.2/0.67	0.91/0.57	S, D	n.d.	+
5	f	67	150/1/0.6	150/1.2/0.67	175/0.92/0.57	150/1.2/0.67	125/0.89/0.56	150/1/0.6	110/1.11/0.6	125/1/0.6	1.04/0.61	S, Sz	n.d.	+
Mean PI/RI*											1.11/0.62			
Mean PI/RI											0.98/0.59			
HUS patients														
6	f	48	100/1/0.6	125/1/0.6	120/0.95/0.58	125/1/0.6	120/0.95/0.58	60/0.95/0.58	75/1/0.6	75/1/0.6	0.98/0.59	normal	n.d.	+
7	f	31	160/0.5/0.38	140/0.6/0.43	200/0.64/0.45	230/0.66/0.45	150/0.43/0.33	110/0.33/0.27	125/0.54/0.4	110/0.65/0.46	0.53/0.39	normal	n.d.	+
8	m	57	80/0.5/0.38	75/0.43/0.33	90/0.63/0.44	90/0.88/0.55	75/0.68/0.47	60/0.75/0.5	60/0.75/0.5	50/0.75/0.5	0.65/0.45	normal	n.d.	+
9	m	31	100/0.75/0.5	80/0.75/0.5	100/0.55/0.4	90/0.88/0.56	100/0.75/0.5	60/0.75/0.5	75/0.68/0.47	50/0.75/0.5	0.74/0.49	normal	n.d.	+
Mean PI/RI											0.72/0.48			

Apostrophe means 6-day follow-up.

CS = Carotid siphon; MCA = middle cerebral artery; ACA = anterior cerebral artery; PCA = posterior cerebral artery; r = right; l = left; n.a. = not available; D = disorientation; S = somnolence; Sz = seizure; DR = decerebration rigidity; C = coma; n.d. = not done; mean PI/RI* = include ACA, MCA and CS of both sides.

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