Evaluation of Cerebral Blood Flow Velocity with Transcranial Doppler Ultrasound in Central Nervous System Infections

Merkezi Sinir Sistemi İnfeksiyonlarında Beyin Kan Akımı Hızının Transkraniyal Doppler ile Değerlendirilmesi

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Abstract: We examined the frequency and clinical relevance of intracranial artery stenoses in patients with central nervous system (CNS) infections in whom the occurrence of stroke has angiographically been reported to be associated with stenoses or occlusions of the cerebral arteries. Thirty-eight patients with CNS infections underwent serial transcranial Doppler (TCD) ultrasound recording of mean blood velocity (MBV) and pulsatility index (PI) in the middle cerebral arteries (MCA), the anterior cerebral arteries (ACA), and the internal carotid arteries (ICA) on days 1, 3, 5, 8, 14, and 21 after admission. The results were correlated with the Glasgow Coma Scale (GCS) (days 1 to 14), and the Glasgow Outcome Scale (GOS) (day 21). A MCA stenosis was diagnosed by a MBV of 120 cm/s or more, or a MCA/ICA ratio of more than 3. An ACA stenosis was diagnosed by a MBV of 100 cm/s or more. In the 12 of 27 bacterial meningitis, a significant increase of MBV in the arteries was recorded, whereas in viral-induced and unclassified infections, no changes of flow velocity were seen. Transient stenoses occurred most frequently between days 3 and 8 and were detected. Patients with stenoses showed a significantly poorer mean GCS score on day 3 than patients without a stenosis. The mean GOS score was not significantly different between both groups. These results suggest that in the early phase, stenoses of the intracranial arteries occur frequently in bacterial meningitis, and are associated with a complicated course of the disease. Non-invasive monitoring by TCD ultrasound may be helpful for early detection of deterioration in cerebral hemodynamic trends.

Key Words: Central nervous system infections, meningitis, stenosis, transcranial Doppler

Özet: Beyin arterlerindeki stenoz ve tıkanmaların anjiyografik olarak inmeyle birlikte seyrettiği gösterilen merkezi sinir sistemi infeksiyonları olan hastalarda kafa içi arter stenozlarının sıklığı ve klinik önemi incelendi. Merkezi sinir sistemi infeksiyonu olan otuz sekiz hastada orta serebral arter, anterior serebral arter ve internal karotid arterde ortalama kan hızı ve pulsatilite indeksi hastanın kabulünden sonraki 1, 3, 5, 8, 14 ve 21. günlerde transkranyal Doppler ultrasonografiyle incelendi. Sonuçlar, Glasgow Koma Ölçeği (GKÖ) (1 ve 14. Günler) ve Glasgow Sonuç Ölçeği (GSÖ) (21. Gün) ile ilişkilendirildi. Orta serebral arter stenozu ölçütleri ortalama kan hızı 120 cm/sn veya daha fazla, 3'ten fazla orta serebral arter/internal karotid arter oranı olarak saptandı. Anterior serebral arter stenozu ölçütü ortalama kan hızı 100 cm/sn veya daha fazla olarak saptandı. Yirmiyedi bakteriyel menenjit olgusunun onikisinde arterlerde ortalama kan hızında anlamlı artış saptandı. Viral veya sınıflandırılamayan infeksiyonlarda akım hızında değişiklik yoktu. Geçici stenozlar en sık olarak 3 ile 8. günler arasında saptandı. Stenozlu hastaların 3. Gün ortalama GKÖ puanı stenozu olmayanlara göre daha düşüktü. Ortalama GSÖ puanı iki grup arasında fark göstermedi. Bu sonuçlar, bakteriyel menenjitte erken dönemde kafa içi arterlerde stenozun sık olduğunu ve bu durumun hastalığın seyrini komplike ettiğini göstermektedir.Traskraniyal Doppler ultrasonografi, merkezi sinir sistemi infeksiyonlarında beyin kan akımındaki bozuklukların erken tanısında yardımcı olabilir.

Anahtar Sözcükler: Menenjit, merkezi sinir sistemi infeksiyonları, stenoz, transkraniyal Doppler

INTRODUCTION

Acute infections of CNS are still diseases with a high mortality rate and a high rate of neurological sequel in the survivors although specific chemotherapeutic agents have dramatically decreased mortality (4,9,25).

Knowledge of pathogenesis, natural course, and the optimal therapeutic management of this complication is still not satisfactory. Earlier angiographic and pathologic studies showed narrowing of intracranial blood vessels as a possible cause of these cerebral ischemic events (10,16). Recently, TCD studies in adult patients with bacterial meningitis (13,14,21,22) described the MBV in the MCA during a period of 3 weeks, showing an increase in MBV within the first week and its normalization toward the third weeks. TCD ultrasound offers a sole possibility to gain insight into the dynamics of cerebrovascular circulation disturbances in cases of CNS infection (3). There have, however, been few published reports on cerebral blood flow (CBF) velocity changes in meningitis (6,10,11,13,14,20-22).

In this study, we examined CBF with the use of transcranial Doppler device in 38 patients with meningitis to determine clinical relevance and frequency of transient stenoses.

PATIENTS AND METHODS

During a 2-year period (1995 to 1996), 38 patients (20 males and 18 females) with CNS infections by various causes were prospectively examined. The age range was 2 to 60 years (mean age 18±15 years). Table I shows the distribution of the infectious agents: 71% were of bacterial origin, and in 5.3% a virus was identified. In 23.7%, the search for the pathogenic agent yielded no result. In most of these cases, however, a viral infection had to be assumed because of specific changes in the cerebrospinal fluid.

Table I: Distribution of the pathogenic agents

Pathogen	No
Bacterial	27
Streptococcus pneumonia	13
Neisseria meningitidis	5
Mycobacterium tuberculosis	3
Brucella spp.	2
Klebsiella spp.	1
Staphylococcus aureus	1
Beta hemolytic streptococcus	1
Enterococcus spp.	1
Viral	2
Herpes simplex	1
Mumps virus	1
Unclassified	9
Total	38

TCD examinations were performed at the bedside by means of a transcranial Doppler device with a 2 or 4 MHz probe (Multi-Dop X, DWL Elektronische Systeme GmbH, Uberlingen, Germany). According to our study protocol, the initial TCD examination was performed within the first 24 hours after admission of the patients. The follow-up TCD examinations were fixed for days 3, 5, 8, 14, and 21 after admission. This included the bilateral insonation of the MCAs and of the ACAs via the temporal approach, and of the ICAs via the submandibular approach according to the technique described by Aaslid et al (2). MBV, the time-averaged maximum velocity over the entire cardiac cycle, was recorded in each artery. As a vascular resistance index the PI was calculated as follows: *PI = (maximum systolic velocity - end-diastolic velocity) / MBV*. A normal MCA recording is shown in Figure 1. Because cerebral hyperemia also elevates the MBV, additionally, the recorded blood velocity waveforms were analyzed according to the absence or presence of the diastolic notch, which was found to be present in blood velocity elevation due to a presumed vasospasm but absent in severely increased blood velocities as a result of hyperemia (7). However, hyperemia increases the MCA/ICA ratio only by approximately 10% (5).

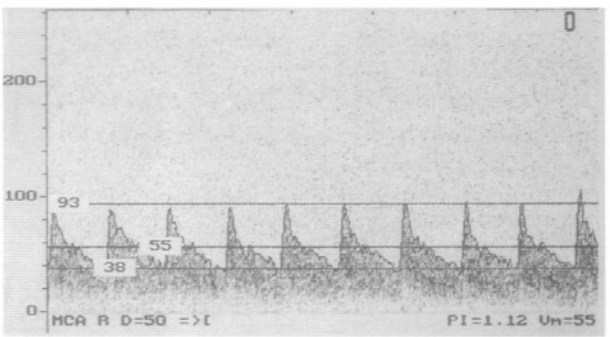


Figure 1. A characteristic normal TCD recording from the MCA. 93 cm/s = maximum systolic velocity; 55 cm/s = mean blood velocity; and 38 cm/s = end-diastolic velocity.

At the time of each TCD recording, the patients were clinically scored with the use of the GCS (27). Additionally, focal cerebral signs such as hemiparesis and aphasia were recorded separately. Because patients with an uncomplicated course of bacterial meningitis have usually recovered after 3 weeks (9), and additionally because most hemodynamic disturbances that occur in bacterial meningitis have normalized within 3 weeks (11,14,21), we chose day 21 after admission to evaluate the short-term outcome using the GOS (17).

In subarachnoid hemorrhage, a MBV in the MCA of 120 cm/s or more, or a MCA/ICA ratio of more than 3 corresponds well with angiographically demonstrated vasospasm (1,19). The criterion used for our patients to indicate a stenosis of the MCA was an MBV in the MCA of 120 cm/s or more, or an MCA/ICA ratio of more than 3. To indicate a stenosis of the ACA, a threshold MBV of 100 cm/s was chosen. The diastolic notch was present in the MCA and ACA blood velocity waveforms.

All values are reported as mean±SD. The courses of the MCA MBV, the MCA PI, the ACA MBV, and GCS were compared with respect to the presence of a stenosis of the relevant artery by the Varian's analysis. Unpaired t test was used to compare the GOS changes between those with and without stenosis. The results of the TCD measurements of the subgroups (bacterial, viral and unclassified) were compared with χ^2 test.

Table II: Transcranial Doppler Finding According to Pathogenic Agents

	No. (%)		
MBV	Bacterial	Viral	Unclassified
Significantly increased	12 (44)	0 (0)	0 (0)
Normal	15 (56)	2 (100)	9 (100)

p>0.05, (2=4.45)

RESULTS

The blood velocity waveforms showed a diastolic notch on all TCD recordings. Thus, hyperemic blood flow was not recorded on any of TCD examination. Nine of the MCAs and 5 of the ACAs showed a stenosis according to our TCD criteria. Two of these showed a stenosis both MCA and ACA. A MCA stenosis occurred bilateraly in 3 patients. An ACA stenosis was bilateral in 2 patients. There was a correlation between the number of narrowed arteries per patient and the causative pathogen. Increased flow velocities were found in 44% of bacterial meningitis. All TCD findings with regard to the type of the infectious agent are summarized in Table II. During the acute stage (on day 3), the MBV increased dramatically and significantly (p<0.07) in the MCAs with stenosis. Additionally, the MBV of the MCAs with stenosis was slightly elevated on days 5 and 8. The MBV and PI of the MCAs and the MBV of the ACAs are shown in Table III, differentiated into MCAs and ACAs with and without stenosis. The PI did not differ

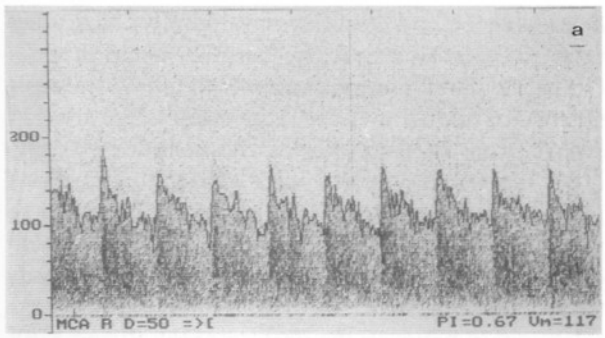
Table III: Course of MBV and PI in the MCA and MBV in the ACA without and with Stenosis and Related to GCS and GOS.

	Day						Statistical
	1	3	5	8	14	21	analysis
MCA MBV, cm/s							
Without stenosis (n=29)	66(17)	68(19)	65(18)	66(14)	64(18)	72(17)	p>0.05 (F=0.37)
With stenosis (n=9)	76(36)	101(28)	85(37)	82(20)	78(26)	58(25)	p<0.07 (F=2.125)
MCA PI							
Without stenosis (n=29)	1.14(0.87)	0.91(0.84)	0.93(0.55)	0.83(0.66)	0.91(0.65)	0.89(0.45)	p>0.05 (F=1.34)
With stenosis (n=9)	1.12(0.70)	0.98(0.45)	0.92(0.89)	0.91(0.73)	0.90(0.45)	0.82(0.34)	p>0.05 (F=0.595)
ACA MBV, cm/s							
Without stenosis (n=33)	53(16)	56(14)	55(14)	54(17)	59(16)	47(15)	p>0.05 (F=1.38)
With stenosis (n=5)	65(32)	79(27)	74(23)	76(19)	64(20)	66(14)	p>0.05 (F=0.376)
GCS							
Without stenosis (n=26)	12.7(1.7)	13.5(1.4)	13.8(1.2)	14.4(0.8)	14.6(0.8)		p<0.0001 (F=7.71)
With stenosis (n=12)	12.5(0.9)	12.6(0.7)	13.3(1.1)	13.7(1.4)	14.1(1.7)		p<0.02 (F=2.72)
GOS							
Without stenosis (n=26)						4.87(0.33)	p>0.05 (F=1.75)
With stenosis (n=12)						4.59(0.67)	

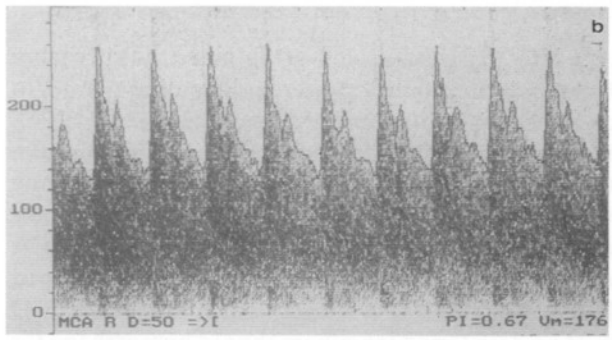
Values are mean(SD

significantly from days 1 to 21 between both groups of MCAs. The MBV of the ACAs with stenosis was slightly elevated on days 3, 5 and 8 ($p>0.05$). The values returned to normal levels usually within 14 days but one patient had returned to his initial values after 21 days.

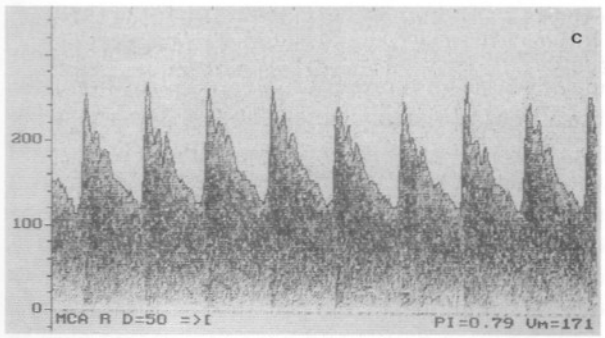
Clinically, a significantly poorer mean GCS score was observed the patients with (12.5±0.9) and without (12.7±1.7) stenoses of the intracranial arteries on day 1. Thereafter, the patients with stenoses of the intracranial arteries exhibited a significantly poorer mean GCS score on day 3 compared with the patients without stenosis of a basal cerebral artery. The occurrence of mainly transient focal cerebral signs was significantly related to the number of narrowed vessels per patient. The causative pathogen had no effect on the GCS scores. The mean GOS scores of the patients without a stenosis of an artery (GOS score, 4.87±0.33) did not differ significantly from those with stenoses (GOS score, 4.59±0.67). A poorer GOS score did not correlate with the causative pathogen (Table III). The time course of stenosis and GCS/GOS were shown in Figure 2 (a-f).



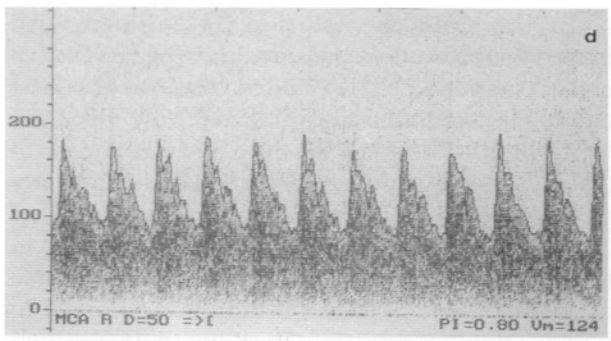
a: day 1, GCS 13



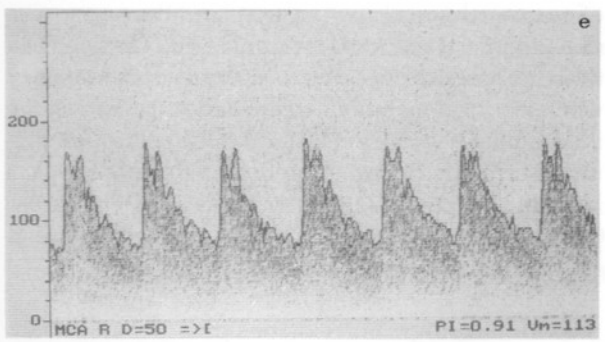
b: day 3, GCS 12



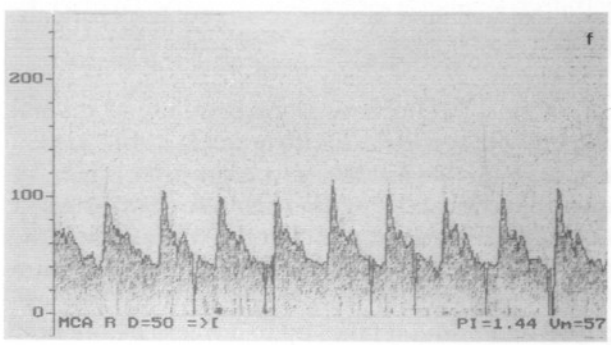
c: day 5, GCS 12



d: day 8, GCS 13



e: day 14, GCS 15



f: day 21, GCS 15

Figure 2. (a-f): Graphic illustration, obtained from a 34-year-old man with Staphylococcus aureus meningitis, shows the relation between blood velocity recording in MCA and GCS/GOS.

DISCUSSION

The vascular complications of bacterial meningitis such as stenosis or occlusion of the cerebral arteries, and thrombosis of the veins or sinus are well known (23). The actual frequency of a stenosis or an occlusion of the basal cerebral arteries in patients with meningitis is certainly unknown. Because of the risks of angiography, a serial angiographic study of patients with bacterial meningitis to clarify the frequency and the clinical relevance of stenoses of the basal cerebral artery is not justifiable.

TCD is now a well-established noninvasive technique for monitoring cerebral hemodynamics in a variety of pathological conditions (1,8,12,14,19,26). However, some of the disadvantages of TCD have to be considered, such as the absence of a bone window, the angle of insonation and the experience of the examiner (21). TCD and angiographic MCA narrowing correlate well in subarachnoid hemorrhage (12,24). It seems justified to use the TCD criteria developed for subarachnoid hemorrhage for the detection of vessel stenosis in meningitis (21).

Our study consisted of 38 patients with bacterial, viral and unclassified meningitis. Twelve of the 38 patients (32%) exhibited a stenosis of at least one basal cerebral artery. Maximal flow velocities were observed between the third and eighth days of disease. Thereafter, the MBV increased significantly on day 3 in the MCAs with stenoses. In 12 (44%) of 27 patients with bacterial meningitis, an increase in flow velocity were observed throughout the course of disease. None of viral infection was observed to increase flow velocity. In patients with unclassified pathogenic agents, a viral infection had to be assumed because of specific changes in the cerebrospinal fluid, was not observed. In all patients, the velocity changes were fully reversible.

These TCD observations correlate in several aspects with reports in the literature (13,14,21,22). On the basis of the literature, our results might be interpreted as showing that stenotic changes occur in the basal intracranial arteries throughout the course of bacterial meningitis. The maximum hemodynamic disturbance is to be expected between days 3 and 8, and it takes up to 3 weeks before flow velocities have returned to normal or to their initial values. Müller et al (21) found that the transient stenoses occurred most frequently between days 3 and 5, and were detected in 51% of patients with bacterial meningitis. Haring et al (14) reported that in viral-induced infections, no changes of flow velocity in basal cerebral arteries were seen, whereas in bacterial meningitis, a significant increase of blood flow velocity in MCA was recorded. Both studies suggest that the stenoses of the intracranial arteries occur frequently in bacterial meningitis and are associated with a complicated course of the disease.

The cause of high flow velocity within a segment that can be reached by TCD may be reduction of blood vessel diameter, reduced cerebral peripheral resistance and increase in global hemispheric blood flow. Several angiographic studies revealed narrowing of the basal cerebral arteries (10,16,23). They demonstrated isolated or multiple stenosis or occlusion of the large intracranial arteries. Apart from the diameter of the insonated artery, other factors may affect MBV. First, a decrease in intracranial pressure (ICP) has been reported to increase MBV as an index of CBF in patients with bacterial meningitis (11,20). An increase in ICP leads to an increase in PI (15,18). There was inverse relationship between the pattern of the PI and MBV (21). In our patients, PIs were within normal value. Second, hyperemia increases MBV (7,26). However, rapid increase of the MCA/ICA ratio is a strong argument against the postulate that the highly elevated MBVs represent hyperemia. Additionally, the absent of diastolic notch suggest hyperemia (7).

Clinically, the occurrence of vessel stenoses was significantly associated with a poorer GCS score on day 3, but significantly poorer mean GCS was observed in patients with and without stenosis on day 1. Additionally, the presence of focal cerebral signs between days 1 and 5 was associated with an increasing number of vessel stenoses. Müller et al (21) found a significant relationship between the number of narrowed vessels per patient, and the occurrence of poorer GCS and focal cerebral signs. They suggest that cerebral ischemia due to arterial narrowing may worsen critical metabolic disturbances caused by the inflammatory process (4,21,25). Our corresponding measurements demonstrated that the poorer GCS score did not correlate with stenoses only. The poorer GOS score did not correlate with the occurrence of stenoses and causative pathogen.

Monitoring CBF velocities provides important information for the treatment of patients suffering from bacterial meningitis. Thus, TCD ultrasound, a noninvasive examination technique, offers a quick and risk-free monitoring device for early recognition

of the patients with meningitis who risk developing cerebrovascular complications. TCD ultrasound is a useful procedure in the evaluation of meningitis and its complications.

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REFERENCES

1. Aaslid R, Huber P, Nornes H: Evaluation of cerebrovascular spasm with transcranial Doppler ultrasound. J Neurosurg 60:37-41, 1984
2. Aaslid R, Markwalder TM, Nornes H: Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg 57:769-774, 1982
3. Aaslid R: Transcranial Doppler examination techniques, in Aaslid R (ed), Transcranial Doppler Sonography, New York, NY: Springer Publishing Co Inc, 1986:39-59
4. Ashwal S, Tomasi L, Schneider S, Perkin R, Thompson J: Bacterial meningitis in children: pathophysiology and treatment. Neurology 42:739-748, 1992
5. Benalcazar HE, Martin NA, Thomas-Lukes K, Rinsky BS: How do transcranial Doppler velocities and the Lindegaard ratio change in hyperemia? A quantitative analysis. Stroke 25:738, 1994
6. Bode H, Harders A: Transient stenoses and occlusions of main cerebral arteries in children: diagnosis and control of therapy by transcranial Doppler sonography. Eur J Pediatr 148:406-411, 1989
7. Chan K-H, Dearden NM, Miller JD, Midgeley S, Piper IR: Transcranial Doppler waveform differences in hyperemic and nonhyperemic patients after severe head injury. Surg Neurol 38:433-436, 1992
8. Chan K-H, Dearden NM, Miller JD: Transcranial Doppler sonography in severe head injury. Acta Neurochir (Wien)Ssuppl 59: 81-85, 1993
9. Durand ML, Calderwood SB, Weber DJ, Miller SI, Southwick FS, Caviness VS, Swartz MN: Acute bacterial meningitis in adults: a review of 493 episodes. N Engl J Med 328:21-28, 1993
10. Gado M, Axley J, Appleton DB, Prensky AL: Angiography in the acute and post-treatment phases of hemophilus influenzae meningitis. Radiology 110:439-444, 1974
11. Goh D, Minns RA: Cerebral blood flow velocity monitoring in pyogenic meningitis. Arch Dis Child 68:111-119, 1993
12. Grosset DG, Straiton J, McDonald I, Cockburn MC, Bullock R: Use of transcranial Doppler sonography to predict development of a delayed ischemic deficit after subarachnoid hemorrhage. J Neurosurg 78:183-187, 1993
13. Grupta R, Mahapatra AK, Bhatia R: Serial transcranial Doppler study in meningitis. Acta Neurochirurgica 137:74-77, 1995
14. Haring H-P, Rötzer H-K, Reindl H, Berek K, Kampfl A, Pfausler B, Schmutzhard E: Time course of cerebral blood flow velocity in central nervous system infections: a transcranial Doppler sonography study. Arch Neurol 50:98-101, 1993
15. Hassler W, Steinmetz H, Gawlowski J: Transcranial Doppler ultrasonography in raised intracranial pressure and in intracranial circulatory arrest. J Neurosurg 68:745-751, 1988
16. Igarashi M, Gilmartin RC, Gerald B, Wilburn F, Jabbour JT: Cerebral arteritis and bacterial meningitis. Arch Neurol 41:531-535, 1984
17. Jennett B, Bond M: Assessment of outcome after severe brain damage: Lancet 1:480-484, 1975
18. Klingelhöfer J, Conrad B, Benecke R, Sander D, Makakis E: Evaluation of intracranial pressure from transcranial Doppler studies in cerebral disease. J Neurol 235:159-162, 1988
19. Lindegaard K-F Nornes H, Bakke SJ, Sorteberg W, Nakstad P: Cerebral vasospasm diagnosis by means of angiography and blood velocity measurements. Acta Neurochir (Wien) 100:12-24, 1989
20. McMenamin JB, Volpe JJ: Bacterial meningitis in infancy: Effects on intracranial pressure and cerebral blood flow velocity. Neurology 34:500-505, 1984
21. Müller M, Merkelbach S, Huss GP, Schimrigk K: Clinical relevance and frequency of transient stenoses of the middle and anterior cerebral arteries in bacterial meningitis. Stroke 26:1399-1403, 1995
22. Müller M, Merkelbach S, Hermes M, Schimrigk K: Transcranial Doppler sonography at the early stage of acute central nervous system infections in adults. Ultrasound Med Biol 22:173-178, 1996
23. Pfister H-W, Borasio GD, Dirnagl U, Bauer M, Einhäupl K-M: Cerebrovascular complications of bacterial meningitis in adults. Neurology 42:1497-1504, 1992
24. Piepgras A, Hagen T, Schmiedek P: Reliable prediction of grade of angiographic vasospasm by transcranial Doppler sonography. Stroke 25:260, 1994
25. Quagliarello V, Scheld WM: Bacterial meningitis: pathogenesis, pathophysiology, and prognosis. N Engl J Med 327:864-872, 1992
26. Steiger H-J, Aaslid R, Stooss R, Seiler RW: Transcranial Doppler monitoring in head injury: relations between type of injury, flow velocity, vasoreactivity, and outcome. Neurosurgery 34:79-86, 1994
27. Teasdale GM, Jennett B: Assessment and prognosis of coma after head injury. Lancet 2:81-84, 1974