NONTRAUMATIC (SPONTANEOUS) SUBARACHNOID HEMORRHAGE

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Summary. *Spontaneous (nontraumatic) subarachnoid hemorrhage (SAH) is an acute and potentially life- threatening condition. There are many conditions and diseases that have been able to bring about SAH but aneurysms play a dominant role. In some percent the cause of SAH still remains undefined . Population based incidence rates vary from 6.5 to 23.9 per 100.000 for all age groups. Many factors have been accepted as risk factors. The amount of extravasated blood correlates well with brain damage and hemodynamic disturbances. Diagnosis must be fast, reliable and the CT is the best method in establishing the diagnosis of intracranial bleeding. The treatment should start as early as possible. The final outcome remains poor for many patients with overall mortality of 25% and many of them will expire due to the initial bleeding.*

Key words: *Subarachnoid hemorrhage, aneurysms, intracranial bleeding*

Spontaneous subarachnoid hemorrhage(SAH) is a potentially life threatening condition. The diagnosis of SAH alerts the physician to discover its etiology, because the cause of SAH will finally determine its management. There are many conditions and diseases able to bring about SAH (Table l) but aneurysms play a dominant role and deserve special attention. On the other hand, to some extent, the cause of SAH will remain undefined (1).

Incidence

Population based incidence rates for SAH vary from 6.5 to 23.9 per 100.000 for all age groups (2, 3), it increases with age (mean age of approximately 50 years), the more frequent is in patients older than 35 years, and is higher in women than in men (4).The aneurysmal SAH is somewhere between 9.3 to 10.8 per 100.000 (5) and the figure is slightly lower in the USA and Canada accounting for 6 to 7 per 100.000.

Table 1. Etiology of spontaneous subarachnoid hemorrhage

Aneurysms..about 75%
AVM...5%
SAH of unknown cause 4%-27%

Other etiological factors

Exotoxins and endotoxins	Moyamoya disease	*Blood diseases*
Sympathomimetic drugs	Fibromuscular dysplasia	Hemophilia
MAO inhibitors	False positive results of LP	Thrombocytopenia
Anticoagulants	Hypertension and/or atherosclerotic disease	Polycythemia
Poisoning by arsenic,	Endocarditis	Sickle-cell anemia
Lead,quinine,CO, morphine	Dural AVM,cavernoma,venous angioma	*Infective diseases*
Amphetamine abuse	Cortical venous thrombosis	Brucellosis
Uremia	Hemorrhagic infarction	Leptospirosis
Systemic collagen vascular diseases (lupus erythematosus, or polyarteritis nodosa)	Alergic reactions	Toxoplasmosis
	Intracranial infections	TBC
Brain tumors	Micotic aneurysms	Herpes zoster
Glioblastomas	Spinal SAH: AVM, aneurysms, tumors	
Pituitary tumors	Primary angiitis and other vasculitis	
Metastatic carcinomas		
Melanomas		

Risk factors

Age, gender, and race have been accepted generally as a risk factor (6) Smoking is a consistent and strong risk factor (7) but still there is a controversy whether tobacco use is a long or short -term risk factor (6). The use of alcohol, especially consummation of large amounts in a short period of time (spree) increases the possibility of SAH (8, 9) Hypertension may be a risk factor, although case control studies do not demonstrate this relationship (10). The use of contraceptive pills was considered to bring about the increase of the incidence of SAH, but recent studies have not supported this hypothesis, although the estrogen composition of these drugs has been changed over time (11). Regarding familiar intracranial aneurysms, it has been suggested that 10% of asymptomatic adult family members of familial intracranial aneurysms families may have aneurysms(12). If SAH appears in one family it is 3-7 times more frequent in siblings (13, 14) so the screening for aneurysms in asymptomatic adults, close relatives of familial intracranial aneurysms can be justified and recommended (12).The rebleeding in SAH, particularly in aneurysmal SAH, is a serious health hazard with a very high mortality and morbidity. It is maximal (4%) on the first day after SAH, and then constant at a rate of 1% to 2% per day over the subsequent 4 weeks (15) .On the other hand, the risk of rebleeding in patients who treated conservatively is between 20% and 30% for the first month after hemorrhage and then stabilizes at a rate of approximately 3% per year (16).

Pathophysiology of SAH

The amount of blood correlates well with the brain damage and hemodynamic disturbances found in patients with SAH. The large ,extraparenhimatous vessels, situated in subarachnoid space are more or less resistant and constrictive under the influence of the extravasated blood. These vessels function as a reservoir of the cerebral perfusion pressure (CPP) important for the maintenance of the cerebral blood flow (CBF). Experimental studies have shown that during the initial bleeding, cerebral autoregulation is functioning. Both autoregulation and CO_2 response are impaired in the acute stage of SAH. (17), and CPP depends directly on the median arterial blood pressure (MABP) and intracranial pressure (ICP) (CPP = MABP - ICP). Regional CBF and cerebral metabolic rate of oxygen (CMRO2) are decreased even in patients with better clinical condition, but is more evident in patients with impaired level of consciousness (18, 19, 20) The brain itself is highly sensitive to the increased metabolic demands, or reduced CBF due to the exhausted reserve capacity of the brain vasculature, which is unable to respond adequately to the increased metabolic demands of the cerebral tissue. The higher level of hemodynamic disturbances, the more severe neurologic deficit and the lower level of consciousness. Serious cellular depolarization can be observed after SAH, followed by disturbed ionic homeostasis, especially in ion K and Ca as well as in neurotransmitters. This ionic disequilibrium affects the numerous aspects of the cellular function in the brain as well as the microvasculature, changing the metabolic activity of the vascular wall and producing the condition for a loss of autoregulation and perhaps playing the leading role in the development of the cerebral edema. (20 ,21). The early occurrence and the long-lasting decrease in Ca 2+-ATPase activity in dogs with experimental SAH induces a persistent disturbance of Ca homeostasis and indicates that damage to the plasma membrane in the cerebral arterial smooth-muscle cells proceeds to myonecrosis after SAH (22). The cerebrospinal fluid (CSF) of patients after different period of SAH bring about a transitory increase of the intracellular, free Ca 2+ in the smooth-muscle cells in the cerebral vessels of the rat ,which is responsible for the contraction of the smooth-muscle of the vascular wall of the large cerebral vessels (22, 23).

Cerebral edema after SAH is probably not ischemic in nature, it has been proved experimentally that the accumulation of water content was extracellulary (24).

There is a controversy concerning the increase of the intracranial pressure(ICP) after SAH. Increased resistance to the CSF inflow was a major contribution to the elevated baseline ICP and a linear correlation between resistance and ICP was confirmed (25, 26).The brain damage after SAH is probably in correlation with the amount of blood in CSF-space consequently exerting the essential influence to the increased ICP and the CPP. The acute increase of the ICP as a result of blood tamponade seems to be the primary cause of the ensuing ischemia (27). There are several factors able to increase ICP: a) the impairment of CSF absorption due to blockade of the arachnoid villi. b) the obstruction of CSF at the basal cisterns, c) cerebral edema and brain infarction, d) the increase of the brain volume or the acute hydrocephalus due to the blocking of the CSF pathways.

Acute hydrocephalus has been observed in about 20% of all patients suffering from SAH and is considered to be the result of acute impairment of CSF absorption. However, even without demonstrable ventricular dilatation it has been shown by CSF outflow resistant studies that CSF absorption may be impaired to a certain degree (28,29) .Thus impairment of CSF absorption seems to be a common pattern after SAH (28).

The increase of concentration of lactic acid, lipid peroxide, with reduction of their scavengers (superoxide dismutase, glutamine peroxidase) after SAH is the result of cerebral hypoxia (30, 31). In the acute stage of SAH, various events such as the initial damage of cerebral vessels, the release of thromboplastin from the damaged brain and the elevation of biogenic amines (epinephrine, norepinephrine, serotonine, etc.) occur in response to

the stress and the stasis of the blood stream and/or systemic dehidration that can predispose to platelet hyperactivity and/or hypercoagulation disorders (32, 33, 34). The high level of noradrenalin is connected to the hypothalamic injury either indirectly, as a consequence of the adrenal gland damage, or directly, due to the increased release of nor-adrenaline by the sympathetic nerve endings (26, 35, 36). There have been few reports to date on DIC in association with SAH (32, 33, 37). However, some authors have reported a high incidence of abnormal coagulation and fibrolytic disorders associated with SAH (38,39,40). It has been reported that the hypercoagulant and hyperfibrinolitic state is often encountered in the acute stage of SAH (39, 41).

Patients with SAH are generally volume-depleted at the time of presentation and this condition can be followed by hyponatremia and increased level of antidiuretic hormone. (42, 43). Morphologic and functional damage to the endothelium, smooth-muscle cells and nerve terminals is a usual consequence of SAH. The growth factor has the main role as well as the insulin- like growth factor derived from platelets, smooth- muscle cells and plasma (43).

Diagnosis

In spite of the established criteria, signs, and symptoms of SAH a disorientation still exist in establishing the diagnosis (44, 45) The case history of SAH can be misinterpreted as meningitis due to the neck stiffness and moderate fever as the result of meningeal irritation after blood extravasation into the subrachnoid space.

Lumbar puncture (LP) has for a long time been the mainstay of diagnosis in these patients. The uniformly bloody CSF in three successive test-tubes with no coagulation in the next fifteen minutes has been considered as SAH. Willkins and Rengachary (46) suggested that bloody CSF with minimal red blood cells (RBC) count, change on serial tubes and without xanthochromia, if within several hours of onset of clinical symptoms; or xanthochromic CSF without excess protein, RBC, or lipids should be accepted as SAH. But there are some drawbacks in this procedure. Lumbar puncture by itself is not without risk. Patients with SAH may harbor an intracerebral hematoma, sometimes localized in the cerebelum, even if they are fully conscious and withdrawal of CSF in large amount may occasionally precipitate brain shift and herniation (47, 48). Patients without neurological signs other than neck stiffness may have a hematoma of at least 30 mm (49). If the blood-stained CSF is found after LP, sometimes the distinction between traumatic tap and intracranial bleeding is not easy to make (47, 49) The rule that after traumatic tap a decrease in RBC in the consecutive tubes exists is widely accepted, but it can occur also in patients with previous bleeding (50). Conversely, a constant number of cells can be seen with

traumatic taps, so "three tube method" can not made firm diagnosis (49). The cytology of the CSF is of limited value because the appearance of eritrophages (as a signs of intracranial bleding) in SCF takes some time and negative cytology does not exclude hemorrhage (50). Therefore it has been suggested (47, 49) that the best method for distinguishing a traumatic tap from genuine bleed is the spectrophotometric examination of the supernatant fluid attained by centrifugation of the CSF for the presence of xanthochromia. Traces of the blood pigments (hemoglobin bin, bilirubin) exclude an artificial bleeding. The oxyhemoglobin may appears two hours after SAH, but it takes more hours for RBC to lyse and xantochromia to develop (at least 12 hours after hemmorhage) (51, 50).

The most reliable method for establishing the diagnosis of SAH is computerized tomography (CT) and it should be done as early as possible. It was stressed that visible blood on CT scan is detected in about 95% of patients with SAH within first 24 hours.This proportion declines to 90% after one day, 86% on the third postictal day, 80% after 5 days, and only 50% after one week (49, 52, 53). According to the reporting series blood no visible on CT scan in patients with SAH of unknown cause varies from 30% to 60% (1) The reason is still unknown:a)the presence of artifacts on CT at the base of the skull; b) the stream of the blood goes down and is very difficult to be detected in the basal cisterns; c) blood is vanishes quickly and is no perceptive on the CT scan in the first 24h after insult; d) the amount of extravasated blood is to small to be identified. In case that blood is not visible on CT scan, LP should be performed at least 12 hours after the attack, revealing uniformy bloody CSF, or xanthochromia, wich can be identified easily within two weeks after the hemorrhage (49,54,). Only 70% of those who experienced SAH will have xanthochromia in the third week, and 40% of such patients will have blood pigmentation in the fourth week. The four-vessel angiography after SAH is mandatory to confirm, or exclude aneurysms, or AV malformations, and should be performed immediately after establishing diagnosis of bleeding especially in patients with grade 1-3 according the Hunt & Hess classification and can be postponed for almost one week in patients considered not to be a candidate for early operation (grade 4 and 5 the same classification). MRI angiography and three-dimensional CT angiography are the alternative methods for confirmation (or exclusion) the above mentioned diagnosis. The accuracy of cerebral angiography should approach 96% if it is technically adequate with proper magnification, and the optimal visualization of the cerebral vasculature.False negative rate of less than 3.8% can be achieved in this procedure (55, 56,57, 58) Magnetic resonance imaging (MRI) is not well for imaging SAH in the acute stage (49). After several days or weeks however when the CT scan has become normal, MRI may detect subpial deposition of hemosiderin near the source of hemorrhage (49).

Transcranial Doppler Ultrasonography is commonly used later after establishing the diagnosis of SAH for follow-up of cerebral vasospasm. A variety of techniques for measuring regional cerebral flow, evoked potential studies ,and EEG have been used for different purposes (59, 60, 61).

Symptomatology

It can be dramatic, appears suddenly as a headache (mild, moderate, or severe), neck pain, sometime transitory loss of consciousness ,photophobia, vomitting, paralysis of some cranial nerves with or without neurologic deficit. Neurologic deficit and the level of consciousness are in direct correlation with the amount of extravasated blood. The gradation of clinical state is important especially in aneurysmal SAH for further prognosis and treatment. There are several gradation but two of them are usually in use for further prognosis and the type of treatment (see Table 2).

Table 2. Grading scale of Hunt and Hess

I	Asymptomatic or mild headache and slight nuchal rigidity
II	Cranial nerve palsy (e.g.III,VII), moderate to severe headache, nuchal rigidity
III	Mild focal deficit, lethargy or confusion
IV	Stupor, moderate to severe hemiparesis, early decerebrate rigidity
V	Deep coma, decerebrate rigidity, moribund appearance

Scale of the Word Federation of Neurosurgeons

WFNS grade	GCS score	Motor deficit
1	15	absent
2	14-13	absent
3	14-13	present
4	12-7	present or absent
5	6-3	present or absent

Treatment

Subarachnoid hemorrhage is a medical emergency and most protocols include bed rest, application of pneumatic stockings (prevention of thrombosis) osmotic diuretics (manitol for the first 72 hours), anticonvulsants, analgetics and Ca2 + blockers (nimodipin) are in routine use for conservative treatment of acute SAH. Hemodynamic monitoring comprises measuring of blood pressure, arterial blood gases, central venous pressure, pulmonary capillary wedge pressure, peripheral vascular resistance, intracranial pressure monitoring, cardiac output, cardiac

index, and is very useful in further management of patients with intracranial bleeding, especially in those with reduced level of consciousness.

The final outcome for those patients remains poor with overall mortality rates of 25% and significant morbidity up to almost 50% (44). Regarding mortality 30% to 40% will expire within the first week, 47% to 58% within the first month (62, 63, 64).The cumulative mortality rates will be 26% after 6 months, and even 46% after 7 years (65, 66) On the other hand roughly 60% of those who have aneurysmal SAH will have good outcome. Unfortunately the high mortality and morbidity rates will predominantly be the result of initial hemorrhage (over 50% of cases); the rest of them will die due to complications of SAH, vasospasm, hydrocephalus, rebleeding, infection,etc.).Even though the Glasgow Outcome Scores (see table 3) are in general use for final score of patients with SAH they are still unsatisfactory in assessing the outcome after SAH. Even patients who have no grossly evident neurologic deficit after SAH frequently have subtle cognitive or neurobehavioral difficulties that impair their social adjustment and ability to return to their previous occupation (67, 68 ,69).

Table 3. The Glasgow outcome scale

Grade	Neurologic status
1	Good recovery; patient can lead full and independent life with or without minimal neurologic deficit
2	Moderately Disabled; patient has neurologic or intellectual impairment but is independent
3	Severely disabled patient, conscious but totally dependent on others to get through daily activities
4	Vegetative survival
5	Dead

Conclusion

Subarachnoid hemorrhage is an acute and potentialy life-threatening condition. Population incidence rate varies from 6.5 to 23.9 per 100.000 for all age group.There are many risk factors which can afect the incidence of SAH. The amount of extravasated blood correlates well with brain damage and hemodynamic disturbances. Diagnosis must be fast, and reliable and the CT is the best method in establishing the diagnosis of intracranial bleeding .As SAH is a medical emergency the treatment must start as early as possible (within 6 hours). The final outcome remains poor for many patients with overall mortality of 25%, many of whom will expire due to the initial bleeding.

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NETRAUMATSKA (SPONTANA) SUBARAHNOIDNA HEMORAGIJA

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Kratak sadržaj: *Netraumatska (spontana) subarahnoidna hemoragija (SAH) je akutno i potencijalno po život ozbiljno stanje. Postoje mnoga stanja i obolenje koja su u vezi sa etilogijom SAH, ali aneurizme mozga imaju dominantnu ulogu.U odredjenom procentu SAH ostaje nepoznate etiologije.Učestalost se kreće za sve starosne grupe od 6.5 do 23.9 slučaja na 100.000 stanovnika. Mnogi faktori okrivljeni su kao rizik faktori za izazivanje SAH. Količina izlivene krvi u saubarahnoidnom prostoru je u dobroj korelaciji sa o{tecenjem mozga i hemodinamskim poreme}ajima. Dijagnoza mora biti brza, pouzdana i CT je najbolja metoda u dokazivanju intrakranijalnog krvavljenja. Lečenje treba započeti brzo. Krajnji ishod je često loš za mnoge pacijente. Mortalitet se kreće do 25%, većina pacijenta egzitiraće zbog inicijalne hemoragije.*

Ključne reči: *Subarahnoidna hemoragija, aneurizme, intrakranijalno krvavljenje*