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Systematic review of the literature on metabolic changes after aneurysmal subarachnoid haemorrhage

Zmiany metaboliczne po krwotoku podpajęczynówkowym z pękniętego tętniaka – systematyczny przegląd piśmiennictwa

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Abstract

Spontaneous subarachnoid haemorrhage accounts for 5% of strokes and it usually affects healthy and active people. It is most often caused by a rupture of an intracranial aneurysm and it bears a great burden of death and further complications, i.e. cerebral vasospasm and hydrocephalus, both of which still pose a great diagnostic and therapeutic challenge for physicians. Management of patients after aneurysmal subarachnoid haemorrhage largely consists of monitoring and prevention of a secondary injury. While some promising modalities of neuromonitoring have not been universally acknowledged yet, novel and less invasive strategies are studied. Metabolomics, which is one of them, is an analysis of all or at least of a large number of small molecule metabolites in a biological sample at one time. Herein we present a systematic literature review on metabolic changes after aneurysmal subarachnoid haemorrhage, with particular emphasis on concentration of excitatory amino acids and free fatty acids in cerebrospinal fluid. Although the literature review demonstrates limited knowledge in this field, it seems to be a beneficial direction for further research. Small molecule metabolites carry out important physiological functions which, however, may convert to deleterious effects under pathological conditions. As they are ubiquitous across the body, they constitute an ideal target for biomarker research.

Keywords: metabolomics, subarachnoid haemorrhage, vasospasm, biomarker

Streszczenie

Samoistny krwotok podpajęczynówkowy jest przyczyną 5% udarów mózgu i zwykle występuje u zdrowych i aktywnych zawodowo osób. Najczęściej jest spowodowany pęknięciem tętniaka wewnątrzczaszkowego, które wiąże się z dużą śmiertelnością i częstymi powikłaniami, m.in. skurczem naczyń mózgowych i wodogłowiem. Stanowią one duże wyzwanie dla lekarzy zarówno w kontekście diagnostyki, jak i leczenia. Postępowanie u chorych po krwotoku podpajęczynówkowym z pękniętego tętniaka w przeważającej części składa się z monitorowania i zapobiegania wtórnemu urazowi mózgu. Obiecujące sposoby prowadzenia neuromonitoringu wciąż nie zyskały powszechnego uznania i badane są nowe i mniej inwazyjne strategie. Jedną z nich jest metabolomika, zajmująca się analizą wszystkich lub dużej liczby metabolitów małocząsteczkowych w próbce biologicznej w jednym czasie. W poniższym przeglądzie piśmiennictwa przedstawiamy doniesienia na temat zmian metabolicznych zachodzących po krwotoku podpajęczynówkowym z pękniętego tętniaka, podkreślając znaczenie pobudzających neuroprzekaźników aminokwasowych oraz wolnych kwasów tłuszczowych w płynie mózgowo-rdzeniowym. Chociaż przegląd piśmiennictwa wskazuje na ograniczoną wiedzę w tej dziedzinie, wydaje się, że jest to obiecujący kierunek badań. Metabolity małocząsteczkowe pełnią w organizmie ważne funkcje fizjologiczne, jednak w warunkach patologicznych mogą być szkodliwe. Ponieważ są w nim wszechobecne, stanowią idealny cel badań nad biomarkerami.

Słowa kluczowe: metabolomika, krwotok podpajęczynówkowy, skurcz naczyń mózgowych, biomarker

INTRODUCTION

Spontaneous subarachnoid haemorrhage (SAH) accounts for 5% of strokes (Feigin et al., 2009; Rosen et al., 2007), and it tends to affect otherwise healthy and active people. It is caused by a rupture of an intracranial aneurysm in 85% of cases (van Gijn et al., 2007) and it bears a great burden of death and morbidity especially from further complications.

Cerebral vasospasm (CVS) is one of the most common complications after SAH (Frontera et al., 2006), and in fact – the least understood one. In the literature, it is defined either as arterial narrowing on digital subtraction angiography (DSA) or simply as neurological deterioration in absence of rebleeding, hydrocephalus or other identifiable cause (e.g. electrolyte disturbances); hence the possible designations, respectively: angiographic CVS or symptomatic CVS. There is scant information concerning its treatment. The only recommendation with "A" level of evidence is prophylactic administration of oral nimodipine to all patients with aneurysmal SAH (aSAH), whereas induction of hypertension, which constitutes a part of haemodynamic augmentation therapy, aka triple-H therapy, was labelled with "B" level of evidence (Connolly et al., 2012).

Hydrocephalus (HCP) occurs in up to 30% of patients after SAH (Germanwala et al., 2010), and requires shunting in nearly half of the cases (Park et al., 2018). Although the presence of acute HCP was clearly associated with higher Fisher grade (Demirgil et al., 2003), independent risk factors for late shunt placement were bleeding from the middle cerebral artery aneurysm and cerebral infarction due to vasospasm (Shigematsu et al., 2016). Both CVS and HCP continue to pose a great diagnostic and therapeutic challenge for physicians (Geraghty and Testai, 2017; Paisan et al., 2018).

Management of patients after aSAH largely consists of monitoring and prevention of a secondary injury (Roh et al., 2016). Although continuous monitoring of the brain function is possible, it requires invasive procedures, i.e. microdialysis via intracerebral microprobes and assessment of cerebral blood flow and brain tissue oxygenation (Arshi et al., 2013; Findlay et al., 2016; Spiotta et al., 2011; Vajkoczy et al., 2003). While these promising modalities have not been universally acknowledged yet, novel and less invasive strategies are studied (Przybycien-Szymanska and Ashley, 2015).

The term "metabolomics" was coined in the recent literature to connote attempts to measure all (or at least a large number) of small molecule metabolites in a biological sample at one time. In reality, its history goes back to pioneering application of analytical chemistry in clinical medicine. In 1927 Warburg et al. described altered glucose metabolism in rat carcinoma on the basis of lactose concentrations in arterial and venous blood, thus laying the foundation for future development of biomarker research.

Liquid chromatography–mass spectrometry became an established technology in the field of metabolomics due to its versatility and robustness (Gika et al., 2014). Some authors have reported its utility in stroke as well (Guo et al., 2019; Laborde et al., 2012). As it is compatible with various materials, i.e. body fluids and tissue homogenates, it gives clear advantage in biomarker research by means of minimally invasive procedures. Detected changes of small molecules concentration may either be an effect of altered metabolism thus having prognostic value, or contribute to secondary brain injury. In the latter case, the use of such a biomarker could prompt administration of adequate treatment before clinical deterioration. In the future it may also constitute an ideal diagnostic tool for screening programs.

REVIEW OF THE LITERATURE

To identify original studies on metabolic changes after aSAH, we performed a PubMed database search using a combination of queries "metabolic," "metabolomic," "subarachnoid," "h(a)emorrhage," and "aneurysm(s)." We excluded reviews, meta-analyses, studies on animals and those focusing on stroke in general. Eventually, we identified 16 original papers, which are summarised in Tab. 1. Various target samples of potential clinical value were considered: cisternal and lumbar cerebrospinal fluid (CSF), arterial and jugular vein blood, serum, plasma, and brain tissue. At first sight, this situation seems to indicate a serious gap in this field of knowledge as well as our efforts to establish a new clinical biomarker.

Concentration of amino acids in CSF was studied most frequently, particularly of excitatory amino acids (EAA) (Barges-Coll et al., 2013; von Holst and Hagenfeldt, 1985; Jung et al., 2013, 2012; Kofler et al., 2015; Li et al., 2018; Lindgren et al., 2014; Lu et al., 2018; Sokół et al., 2017; Staub et al., 2000;). In 1995 Bullock et al. demonstrated a release of glutamate and aspartate to the brain tissue in a patient after occlusive stroke. It prompted further research on excitatory neurotransmitters antagonists as neuroprotective agents (Myseros and Bullock, 1995; Turski et al., 1998), which failed to provide clinical benefit, though (Chen and Wang, 2016). Still, in symptomatic CVS a decrease in regional cerebral blood flow correlated with extracellular concentration of EAA (Sarrafzadeh et al., 2004), and there was clear evidence that it is much greater in ischemia as compared with penumbra or noninfarcted brain tissue (Berger et al., 2002; Sahu et al., 2017). Kett-White et al. (2005) set a threshold of cerebral tissue oxygen pressure that induced metabolic changes after stroke. Interestingly enough, Hutchinson et al. (2002) indicated that an increase in EAA levels happens together with an increase in concentration of inhibitory amino acids, notably γ-aminobutyric acid (GABA), and suggested possible therapeutic effect of exogenous GABA agonists. At that time, Globus et al. (1991) had already suggested the usage of so-called excitotoxic index as a biomarker of neuronal vulnerability, which appeared useful in detecting patients with lacunar infarcts who had been experiencing motor function deterioration (Serena et al., 2001).

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Year	Authors	Origin	Study group	Controls	Material	Conclusion
1985	von Holst and Hagenfeldt	Sweden	26	0	CSF-L and CSF-C	• Increased concentration of amino acids in CSF after aSAH may result from proteolysis due to catabolic processes, and from impaired clearance of amino acids from CSF
1988	Paoletti et al.	Italy	48	12	CSF-L and CSF-C	• Enhanced metabolism of arachidonic acid via the lipoxygenase pathway was associated with aSAH • Increased concentration of leukotriene C_4 in CSF was associated with occurrence of symptomatic CVS
1992	Gaetani et al.	Italy	13	5	Straight gyrus	• Enhanced metabolism of arachidonic acid in human brain tissue was associated with aSAH
2000	Staub et al.	Germany	10	0	CSF-C	• Increased concentration of excitatory amino acids and lactate in CSF was associated with poor outcome after aSAH
2002	Pilitsis et al.	USA	20	73	CSF-L or CSF-C	• Increased concentration of free fatty acids in CSF was associated with occurrence of angiographic CVS
2012	Jung et al.	Germany	30	6	CSF-C	• Increased concentration of ADMA in CSF was associated with occurrence of angiographic CVS
2013	Jung et al.	Germany	18	5	CSF-C Serum	• Increased concentration of glutamate, glutamine, glycine, and histidine in CSF was associated with occurrence of angiographic CVS
2013	Barges-Coll et al.	Mexico	40	18	Plasma	• Increased concentration of taurine in plasma was associated with poor outcome
2013	Barcelos et al.	France	68	0	Blood from jugular and radial catheters	• Decreased metabolic ratio and increased lactate-oxygen index were associated with poor outcome after aSAH
2014	Lindgren et al.	Sweden	56	112	Serum	• Increased concentration of ADMA in serum was associated with aSAH and particularly with poor outcome • Decreased arginine/ADMA ratio in serum after aSAH was associated with poor outcome
2014	Kurtz et al.	USA	28	0	Blood	• Increased systemic glucose variability was associated with mortality after severe aSAH
2015	Kofler et al.	Austria	25	0	ECF	• Increased concentration of taurine in ECF after aSAH was associated with delayed cerebral infarction
2015	Sjöberg et al.	Sweden	50	0	Serum	• Increased concentration of myo-inositol in serum after aSAH was associated with good outcome
2017	Sokół et al.	Poland	23	25	CSF-C	• Increased concentration of amino acids in CSF was associated with aSAH • Concentration of amino acids in CSF increased up to 10 days after aSAH • Increased concentration of excitatory amino acids in CSF after aSAH was associated with poor outcome
2018	Li et al.	China	40	6	CSF-L or CSF-C	• Increased concentration of pyruvic acid and decreased concentration of 2-phosphoglyceric acid, and 3-phosphoglyceric acid in CSF after aSAH were indicators of high score in Hunt–Hess scale • Increased concentration of aspartate, asparagine, methionine, phenylalanine, tryptophan, leucine, isoleucine, ornithine, tyrosine, phenylpyruvate, serine, glycine, threonine, valine, alanine, histidine, 3-phospho-serine, homoserine, homocysteine, homocysteic acid, glutamate, glutamine, and ornithine in CSF after aSAH was associated with poor outcome
2018	Lu et al.	USA	15	0	CFS-C	• Increased concentration of 2-hydroxyglutarate, tryptophan, glycine, proline, isoleucine, and alanine in CSF after aSAH was associated with poor outcome

CSF-C – central cerebrospinal fluid; **CSF-L** – lumbar cerebrospinal fluid; **aSAH** – aneurysmal subarachnoid haemorrhage; **CSF** – cerebrospinal fluid; **CVS** – cerebral vasospasm; **ADMA** – asymmetric dimethyl-L-arginine; **ECF** – brain extracellular fluid.

Tab. 1. Review of the literature on metabolic changes in body fluids after aSAH

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In 1992 Gaetani et al. demonstrated that arachidonate metabolism in brain tissue is enhanced after SAH (Gaetani et al., 1992), which was later confirmed (Pilitsis et al., 2002; Poloyac et al., 2005). It is suspected that initial efflux of free fatty acids (FFA) into CSF after aSAH underlies the mechanism of CVS through an increase in intracellular calcium concentration (Jaskólski and Zawirski, 1988; Pilitsis et al., 2002). In patients after stroke, high level of FFA in CSF appeared to be an independent risk factor of unfavourable outcome, was associated with increased mortality (Wei et al., 2015), and recurrence in a 1-year follow-up (Wang et al., 2016). The level was higher after cardioembolic ischaemia (Sun et al., 2015). Serum FFA level was associated with unfavourable outcome after stroke as well (Duan et al., 2017). Preclinical evidence has demonstrated that inhibition of synthesis of 20-hydroxyeicosatetraenoic acid (20-HETE), a product of omega-oxidation of arachidonic acid, reduced the size of infarct in an animal stroke model (Marumo et al., 2010; Miyata et al., 2005). In addition, detectible 20-HETE level in CSF was associated with poor outcome after aSAH (Crago et al., 2011). Recently, Nakagawa et al. (2017) observed reduced frequency of CVS in patients after aSAH treated with omega-3 fatty acids.

In 2014 Kurtz et al. demonstrated that increased systemic glucose variability may be associated with mortality after severe aSAH (Kurtz et al., 2014). In contrast to the previously mentioned findings, this one concerns general neurocritical care rather than presence of specific complications after aSAH (Krinsley, 2008). In contrast to the poor-prognosis factors, increased concentration of myo-inositol in serum after aSAH appeared associated with good outcome (Sjöberg et al., 2015). Eventually, in 2018 Li et al. showed that increased concentration of pyruvic acid and decreased concentration of 2-phosphoglyceric acid, and 3-phosphoglyceric acid in CSF after aSAH were indicators of high score in Hunt–Hess scale (Li et al., 2018).

It is also important to indicate some protein-derived biomarkers in patients after aSAH. Various authors observed that an increased S100 protein level in both CSF and serum after aSAH may be associated with poor outcome and particularly with occurrence of cerebral infarction (Hårdemark et al., 1989; Jung et al., 2013; Moritz et al., 2010; Takayasu et al., 1985). What is more, Kacira et al. (2007) revealed increased concentration of caspase-3, neuron-specific enolase (NSE), and high-sensitivity C-reactive protein in both CSF and serum in patients after aSAH and commented that NSE level in CSF may be associated with poor outcome and occurrence of cerebral infarction. On the other hand, Bellapart et al. (2014) denied any association between NSE or S100 and occurrence of CVS after aSAH, and suggested measurement of serial plasma endothelin-1 concentration as a potential screening marker of vasospasm.

CONCLUSIONS

Although the literature review demonstrates limited knowledge in the field of metabolic changes after aSAH, it seems to be a promising direction for further research. Small molecule metabolites carry out important physiological functions which convert to deleterious effects under pathological conditions. As they are ubiquitous across the body, they constitute an ideal target for research on biomarkers.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

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