The Role of CSF-Isolated Microparticle-Derived Mechano-Growth Factor (MGF) in the Development of Cerebral Vasospasm Post aSAH

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Learning Objectives

To understand the role of MGF in the development of CV post aSAH.

Introduction

Cerebral vasospasm (CV) and related ischemic injury is a major contributor to death and disability after aneurysmal subarachnoid hemorrhage (aSAH). Mechano-growth -factor (MGF) - a splice variant of insulin-like growth factor 1 (IGF-1) - has been shown to exhibit neuroprotective effects, as well as upregulate heme oxygenase 1 (HO-1). Our goal is to understand the molecular mechanisms underlying CV and the role of MGF in the development of CV to develop of safe and effective diagnostic and treatment paradigms for CV. We hypothesize that specific early changes in microparticle-derived MGF mRNA and protein expression attenuate CV development and/or reduce associated morbidity and mortality.

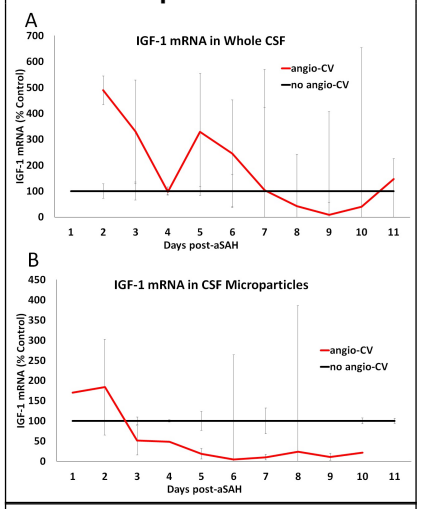
Methods

-Cerebro-spinal fluid (CSF) was collected daily from patients with aSAH.
-Total RNA and protein were isolated from whole CSF and from microparticle (MP) fractions
-MP were isolated from whole CSF using serial ultracentrifugation at 4°C.
-Differential mRNA and protein expression in whole CSF and CSF-MPs measured with qRT-PCR and ELISA. mRNA and protein levels were correlated with clinical data and used to identify candidates for pathological and/or neuroprotective pathways activated in development and progression of CV. All data expressed as % control (non-CV) ± SEM

Patient Demographics

Patient	Gender	Age	H-H Scale	Fisher Grade	aSAH	Angio-CV	Clinical-CV
1	F	59	2	3/4	Yes	mild	mild
2	F	73	2	3/4	Yes		
3	F	44	N/A		No		
4	F	49	2	3/4	Yes	Severe	No
5	M	39	N/A		No		
6	F	54	4	3/4	Yes		
7	F	51	3	3/4	Yes	Mild	No
8	M	62	2	2	Yes		
9	F	53	5	3	Yes	Severe	Deceased
Average		53.7±10	2.84±1.21	3.2±0.57			

IGF-1 mRNA in CSF of aSAH patients



MGF mRNA in CSF of aSAH patients

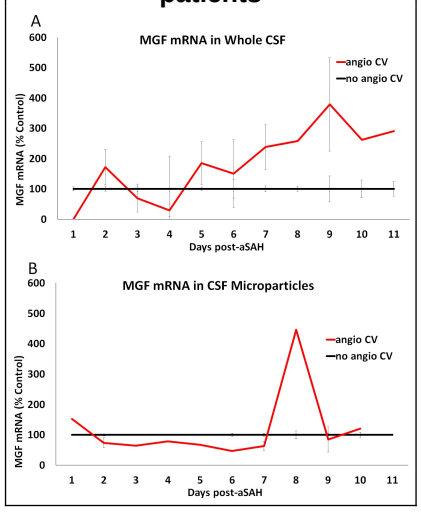


Table 1. Demographic data from patients with aSAH, 2 patients were diagnosed with severe angiographic CV (angio -CV) and remaining patients had mid or no CV (non-angio. CV group)

Fig 1. IGF-1 mRNA in whole CSF (A) and in CSF-isolated Microparticles (B) from patients with severe (n=2) and without (n=7) severe angiographic CV post aSAH.

IGF-1 mRNA in whole CSF was higher prior to the onset (days 5-6) and lower following the onset (days 8-10) of severe angio-CV in CV patients; IGF-1 mRNA in MP fraction was lower in severe angio-CV patients and no correlation with the onset of CV was observed.

Fig 2. MGF mRNA in whole CSF (A) and in CSF-isolated Microparticles (B) from patients with severe (n=2) and without (n=7) severe angiographic CV post aSAH.

Peak in MGF mRNA in both whole CSF and CSP MP was observed around 8th day post -aSAH which correlated with the onset of CV.

HO-1 expression in CSF of aSAH patients

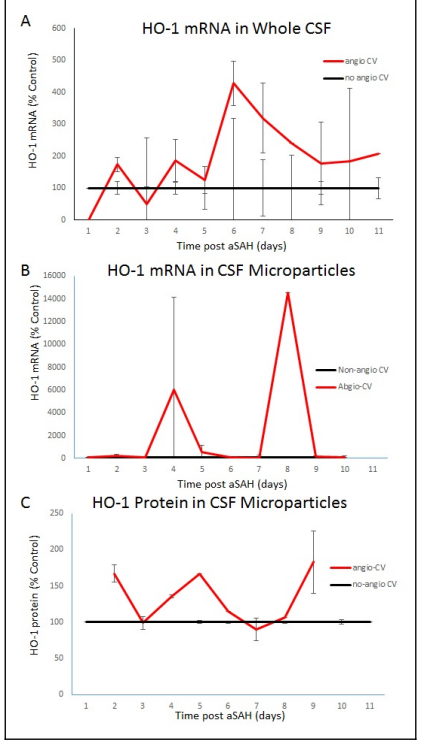


Fig 3. HO-1 mRNA in whole CSF (A), HO-1 mRNA in CSF-isolated Microparticles (B), and HO-1 protein in CSF-isolated Microparticles (C) from patients with severe (n=2) and without (n=7) severe angiographic CV post aSAH.

In MP-fraction, levels of HO-1 protein (C) peaked on days 5 and 9 post aSAH, one day after respective increase in mRNA levels (B). These changes correlated with the onset of sever CV and increased expression of MGF mRNA in MP (Fig. 2B).

Results

IGF-1 mRNA expression in whole CSF and CSF-MP isolated from severe CV patients did not correlate with the onset or progression of CV.

MGF and HO-1 mRNA expression in whole CSF samples did not correlate with the onset but correlated with the progression of severe CV.

MGF and HO-1 mRNA expression in CSF-MP correlated with the onset of severe CV. HO-1 protein expression in MP followed MGF and HO-1 mRNA expression patterns.

Conclusions

MGF may act through neuroprotective HO-1 pathway. This pathway may be associated with the onset and progression of severe CV in aSAH patients however; further studies need to be performed to elucidate the role of MGF and HO-1 in patients with severe CV post aSAH.