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Clinical Study

Elevated cerebrospinal fluid and serum YKL-40 levels are not associated with symptomatic vasospasm in patients with aneurysmal subarachnoid haemorrhage

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Abstract

YKL-40 is a newly discovered matrix protein that is thought to be released during the acute stages of inflammation. It has recently been speculated that YKL-40 may serve as a specific serological marker of neutrophil function at the site of tissue inflammation. Our aim was to determine whether the levels of YKL-40 in both the cerebrospinal fluid and sera of 22 patients with aneurysmal subarachnoid haemorrhage were associated with either vasospasm or outcome. The levels were also compared with those of 16 control patients with hydrocephalus. We found that patients with aneurysmal subarachnoid haemorrhage had significantly higher YKL-40 levels in both cerebrospinal fluid and serum than controls. However, elevated YKL-40 levels were not associated with symptomatic vasospasm or 6-month outcome. We show that elevated YKL-40 levels are not correlated with the severity of subarachnoid haemorrhage and cannot be used as a serological marker of inflammation in patients with an aneurysm rupture.

Keywords: Aneurysm; Inflammation; Subarachnoid haemorrhage; Vasospasm; YKL-40

1. Introduction

Despite recent advances in both the diagnosis and treatment of cerebral vasospasm (VS) following ruptured cerebral aneurysm, it still remains one of the most challenging clinical conditions for neurosurgeons. An association between the release of blood breakdown products[1] and adhesion molecules in the subarachnoid space and VS has been established;[2–5] however, the precise pathophysiological mechanisms leading to cerebral VS remain unclear. The matrix protein YKL-40 is a member of the 18-glycosylhydrolase family and is a heparin- and chitin-binding lectin without chitinase activity.[6] Its name is derived from the one-letter code for its first three N-terminal amino acids and from its molecular weight of 40 kDa.[7] The gene coding for YKL-40 is known, but the exact physiological function of YKL-40 remains unknown.[8] However, the pattern of its expression in normal and pathological states suggests that it plays a role in the inflammatory process and may have a function in tissue remodeling.[9–11] YKL-40 is also synthesised by activated macrophages[12] and chondrocyte-synovial cells in patients with rheumatoid arthritis.[13] A positive correlation between the severity of the disease state and the level of YKL-40 in either cerebrospinal fluid (CSF) or sera of patients with a variety of pathological conditions has been demonstrated in recent clinical studies, and most have speculated that YKL-40 might be a valuable biochemical marker of inflammation, similar to C-reactive protein (CRP).[9–11,14–28] We have previously demonstrated that YKL-40 is elevated in both the CSF and sera of patients

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with aneurysmal subarachnoid haemorrhage (SAH) when compared with control patients with normal pressure hydrocephalus.[29] Because our previous work involved a small number of patients, we could not speculate whether there was an association between YKL-40 levels and symptomatic VS (S-VS), in which the putative role of inflammation after aneurysmal SAH is well-known. In the present prospective clinical study, we added 12 more SAH patients to our previous 10 SAH patients,[29] and the results were compared with those for 16 controls with hydrocephalus. At this time, are able to speculate whether there is an association between S-VS and CSF or serum levels of YKL-40. We also added six controls with normal pressure hydrocephalus, who were treated with ventriculo-peritoneal shunting, to our previous 10 controls.[29]

2. Patients and methods

2.1. Patients

Ethical approval for this study was obtained from the Human Investigations Committee at Istanbul University, and all patients or the next of kin if the patient was unconscious provided informed consent. This study involved two groups of patients: (1) 10 patients, as mentioned in a previous work, who were referred to our neurosurgical unit between January and June 2003,[29] and (2) 12 new patients, referred to our neurosurgical unit between February and December 2004, with SAH as established by CT scan. We excluded patients who had any kind of infection, in which YKL-40 may have been involved, at the time of CSF and serum collection. The sole inclusion criterion was admission of the patients to our unit within the first 3 days of SAH (no VS is expected to occur during this time).

2.2. Demographic characteristics of patients and controls

This study included 22 patients with aneurysmal SAH and 16 control patients with hydrocephalus. Of the 16 controls, 13 had normal pressure hydrocephalus and three had hydrocephalus secondary to aqueduct stenosis without any other known central nervous system diseases. The patient group included 13 females and nine males, with a mean age of 49.5 ± 15 years; the control group comprised 8 females and 8 males with a mean age of 55.5 ± 21 years. A summary of the demographic data of the SAH patients is provided in Table 1.

2.3. Specimen handling

From 10 patients, serial blood and CSF samples were collected at the same time within the first 3 days of SAH, and on day 7 of SAH.[29] From the 12 new SAH patients, in addition to these same samples, we also collected CSF and serum samples on day 5 after SAH. Blood and CSF samples were collected via venipuncture and lumbar puncture, respectively. From the control group, blood samples were collected via venipuncture, and CSF samples were obtained while ventriculo-peritoneal shunting was being performed. The samples from the control group were obtained once. As soon as possible, each 10 mL CSF and blood specimen was centrifuged at 10 000 r.p.m. for 15 min and the supernatant was stored at −70 °C until use.

Table 1
Clinical characteristics of patients with SAH

Patient no.	Age/sex	H-H	FG	S-VS	Aneurysm	GOS[a]
1	65/F	III	2	Yes	PCoA	Death
2	67/F	II	3	No	ACoA	GR
3	58/M	III	3	Yes	ICA	SD
4	71/F	V	3	Yes	MCA	Death
5	67/F	II	3	Yes	PCoA	Death
6	56/F	III	3	Yes	OA	SD
7	36/M	II	3	No	ACoA, MCA	GR
8	52/F	II	2	No	MCA	GR
9	43/F	II	2	No	PCoA	GR
10	32/M	III	3	No	ACoA	Death
11	65/F	II	2	Yes	ACoA	Death
12	35/M	II	2	No	ICA	GR
13	65/F	V	4	No	ACoA	Death
14	40/F	II	4	Yes	OA	MD
15	32/M	II	2	No	ACoA	GR
16	48/M	III	2	No	PCoA	GR
17	56/F	II	2	No	OA	GR
18	23/F	II	2	No	ICA	GR
19	44/F	III	1	No	PCoA	MD
20	57/F	II	3	Yes	ICA	PVS
21	56/F	III	3	No	ACoA	Death
22	21/M	I	1	No	BA	GR

The first 10 patients were enrolled in our previous study.[29]
[a] Glasgow outcome scale score at 6 months. ACoA, anterior communicating artery; BA, basilar artery; FG, Fisher grade; GR, good recovery; H-H, Hunt-Hess grade; ICA, internal carotid artery; PCoA, posterior communicating artery; MCA, middle cerebral artery; MD, mild disability; OA, ophthalmic artery; PVS, persistent vegetative state; SD, severe disability; S-VS, symptomatic vasospasm.

2.4. YKL-40 measurement

CSF and serum YKL-40 levels were quantitatively measured in ng/mL. YKL-40 was assayed by a sandwich immunoassay using a microtitre stripwell format (Chondrex; Metra Biosystems, Mountain View, CA, USA). In this system, the Fab fragment of a monoclonal anti-YKL-40 antibody conjugated to biotin binds to streptavidin on the strip and captures YKL-40. A conjugated polyclonal anti-YKL-40 antibody conjugated with alkaline phosphatase binds to the captured YKL-40. Bound enzyme activity is detected with p-nitrophenyl phosphate as substrate. The intra-assay coefficient of variation was less than 7%.

2.5. Statistical analysis

Data were analyzed using SPSS software (version 11.0; SPSS, Chicago, Illinois, USA). Comparisons between patients and controls were carried out using the Mann–Whitney *U*-test and the differences within each group were