Author’s response to reviews

Title: High serum levels of caspase-cleaved cytokeratin-18 are associated with malignant middle cerebral artery infarction patient mortality

Authors:

Leonardo Lorente (lorentemartin@msn.com)
María Martín (mar.martinvelasco@gmail.com)
Antonia Pérez-Cejas (aperezcejas@gmail.com)
Luis Ramos (lramosgomez@gmail.com)
Mónica Argueso (moni_begasa@hotmail.com)
Jordi Solé-Violán (jsolvio@gobiernodecanarias.org)
Juan Cáceres (juanJose.caceresagra@gobiernodecanarias.org)
Alejandro Jiménez (ajimenezsosa@gmail.com)
Victor García-Marín (vicgarmar666@gmail.com)

Version: 2 Date: 20 Dec 2017

Author’s response to reviews:

Dear Editor in Chief

Thank you very much for your comments and the opportunity to send a revised version of our manuscript. We would like, also, to thank the reviewers’ comments, which have helped us to improve our manuscript. The points that we have modified in the manuscript are marked in red color. We enclose the answer to editor and each reviewer and the new version of the manuscript.

Best regards.

Dr. Leonardo Lorente

Response to Reviewer 1 (Pei Xu):

Thank you for your positive comments.
Response to Reviewer 2 (Yangkun Chen):

In general, this study provided a novel investigation of the association between CCCK-18 and mortality of patients with malignant MCA infarction. The design and analyses are sound. However, there are some issues concerned.

1. Introduction

According to the recruited subjects, the aim should be limited to 'malignant MCA infarction' rather than ischemic stroke. Thus, it should be clearly demonstrated.

As was suggested by the reviewer, we have limited the aim to patients with malignant middle cerebral artery infarction (MMCAI).

2. Methods

Were the subjects recruited consecutively? These should be added.

Exclusion criteria were not clear. Should symptomatic ICH/SAH be excluded? Other co-morbid diseases, COPD? Heart failure? Other CNS disease? These should be confirmed.

We have not data about how many patients were excluded from the study and the motivation for the exclusion; thus, we have added this point as another limitation of our study.

We specified that patients with intracerebral hemorrhage or subarachnoid hemorrhage were excluded.

As was suggested by the reviewer in this question and in the next question, we have added in table 1 the information about arterial hypertension, diabetes mellitus, chronic renal failure, chronic obstructive pulmonary disease, heart failure and haemorrhagic transformation.

3. Variables

The mortality of a large territory stroke may be associated with a number of factors. The studied factors in the study might not be adequate. For example, history (hypertension, diabetes, smoking, BP at admission, AF, heart disease, some laboratory results (BNP, HbA1C, etc), as well as whether there was a haemorrhagic transformation. These information is important for mortality in MMCAI.

As was suggested by the reviewer in this question and in the before question, we have added in table 1 the information about arterial hypertension, diabetes mellitus, chronic renal failure, chronic obstructive pulmonary disease, heart failure and haemorrhagic transformation.
Discussion

The interpretation of mechanism underlying this result was too simple and the authors only stated that facts only again.

As was suggested by the reviewer, we have added the following paragraph about our interpretation: “The interpretation of all those findings is uncertain. Cytokeratin-18 exists mainly in the intracytoplasmic cytoskeleton of epithelial tissue and during apoptosis citokeratin-18 is cleaved by caspases and appears as CCCK-18 into the blood [14,15]. Then the question about the origen of CCCK-18 in patients with traumatic brain injury [28], spontaneous cerebral hemorrhage [29,30], and cerebral infarction (our current study) arise now. There is two posible splanations for that question. First, that there is cytokeratin-18 in brain; and this has been found in a study of patients with pituitary adenomas [36], and in a study of rats with glioma [37]. In the study by Luiciani et al was found CCCK-18 in cell extracts of patients with pituitary adenomas, and the use of octreotide induced apoptosis in cells of growth hormone-secreting tumors assessed by the increased of CCCK-18 in cell extracts [36]. In the study by Adri et al was found CCCK-18 in cell extracts of patients with pituitary adenomas, and the use of Parmelia sulcata Taylor (one of the most common lichens that lives mainly in the bark of the trees) induced apoptosis in cell tumors assessed by the increased of CCCK-18 in cell extracts [37]. Second, that MMCAI may cause a systemic inflammatory response syndrome (SIRS), and this could activate sistemic cellular apoptosis. In fact, there are studies reporting SIRS after cerebral infarction [38-40], and in SIRS appears different pro-inflammatory cytokines [41] that could activate apoptosis [2-7].”

We have added the following new references:


