Majorensis 2015; **11**: 49-53 www.majorensis.es

Majorensis
ISSN 1697-5529

CSF biomarkers proposed in Alzheimer´s disease coincide with those found in a rat model of arterial hypertension

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Received: 02-06-2015; Revised: 30-07-2015; Accepted 05-08-2015; Published: 31-12-2015

Summary

CSF biomarkers proposed in Alzheimer´s disease coincide with those found in a rat model of arterial hypertension.

Cerebrospinal fluid is a system linked to the brain and its composition can be altered not only by encephalic disorder such as Alzheimer´s disease (AD) but also by systemic diseases such as arterial hypertension. High blood pressure (HBP) in spontaneously hypertensive rats (SHR) induces alterations in choroid plexus (CP) protein secretion and disruption of the blood-to-cerebrospinal fluid barrier (BCSFB) leading to changes in cerebrospinal fluid protein composition. Reduced CSF levels of the 42 amino acid form of amyloid-beta and increased CSF levels of total tau in AD have been found in numerous studies as AD biomarkers. In other hand, it has been described other biomarkers that are associated with transport through brain barriers and choroid plexus secretion. Thus, several authors have described that: transthyretin, apolipoprotein E, transferrin, α-2-HS-glycoprotein, α-1β-glycoprotein and kininogen are decrease in both AD and HBP compared their controls; α-1-antitrypsin, heavy chain of immunoglobulin G, albumin, vitamin D binding protein and haptoglobin are increased in both AD and HBP compared with their controls. Only apolipoprotein A1 have been described increased in HBP and decreased in AD compared with control. These CSF protein changes could be due to alteration in the BCSFB and in CP described for both AD and HBP pathologies.

Key words: Alzheimer´s disease, high blood pressure, cerebrospinal fluid biomarkers

Resumen

Biomarcadores del CSF propuestos para la enfermedad de Alzheimer coinciden con los encontradas en un modelo de rata hipertensa

Biomarcadores de LCR propuestos en la enfermedad de Alzheimer coinciden con los encontrados en el LCR de un modelo de rata de la hipertensión arterial.

El líquido cefalorraquídeo es un sistema íntimamente relacionado con el cerebro y su composición se puede alterar no sólo por el trastorno encefálico, tales como la enfermedad de Alzheimer (EA), sino también por enfermedades sistémicas tales como la hipertensión arterial. La hipertensión arterial (HTA) en ratas espontáneamente hipertensas (SHR) induce alteraciones en el plexo coroideo (CP), en la secreción de proteínas y en la barrera de sangre-líquido cefalorraquídeo (BSLCR), que lleva a cambios en la composición de las proteínas en el líquido cefalorraquídeo. La reducción de los niveles, en el LCR, del beta-amiloide-42 y de la TAU se describe como biomarcadores de la EA. Por otro lado, se ha descrito otros biomarcadores que están asociados con el transporte a través de barreras cerebrales y la secreción de plexo coroideo. Asimismo, varios autores han observado que: la transtiretina, apolipoproteína E, trans-ferrina, α-2-HS-glicoproteína, α-1β-glicoproteína y quininógeno están disminuidos tanto en EA como HTA al compararon sus controles. En cambio, la α-1-antitripsina, la cadena pesada de la inmunoglobulina G, la albúmina, la proteína de unión a la vitamina D y la haptoglobina están incrementados tanto en EA y HTA al compararlos con sus controles D. Solamente la apolipoproteína A1 se ha descrito aumentada en la HTA y la disminución en el EA. Estos cambios en las proteínas del LCR podrían ser debidos a la alteración en la BSLCR y en los PC descritos tanto para la EA como para la HTA.

Palabras clave: Enfermedad de Alzheimer, Hipertensión arterial, Biomarcadores del líquido cefalorraquídeo

Majorensis
ISSN 1697-5529

Introduction

CSF is a functional system closely connected to the brain, and variations in the CSF composition could mean an alteration in the brain as an expression of brain disorders. However, the composition of CSF may also be altered by systemic diseases, such as arterial hypertension, in SHR, cerebral ventricular dilatation, changes in CSF protein profile and variations in CP have been described [4,7,14, 20,24, 32].

The brain is one of the first target organs of high blood pressure, which is the main modifiable risk factor for stroke. Hypertension causes a progressive increase in cerebral blood flow in the blood vessels of the brain that perform complex and dynamic relationships between blood pressure and brain function. Elevated blood pressure can accelerate atherosclerotic changes and compromise cerebral autoregulation [11]. On the other hand; epidemiological studies link cardiovascular risk factors like hypertension and high plasma cholesterol to dementia. The modulation of the degradation of amyloid precursor protein by the administration of cholesterol in cell cultures and animal models of beta-amyloid overproduction has been described [26], and a connection between inflammation, hypertension and beta-amyloid accumulation has also been reported [5].

La neuroinflamación está asociada con la enfermedad de Alzheimer (EA), nuevos estudios preclínicos y clínicos han establecido que acciones mediadas por el sistema inmune, contribuyen a la patogénesis y desarrollo de la EA. Además, la inflamación en la EA se refiere principalmente al sistema inmune congénito a diferencia de en las enfermedades neuroinflammatorias típicas [19].

The neuroinflammation that is associated with AD has been assumed to be merely a response to pathophysiological events. New data from preclinical and clinical studies have established that immune system-mediated actions in fact contribute to and drive AD pathogenesis. In addition, as inflammation in AD primarily concerns the innate immune system unlike in 'typical' neuro-inflammatory diseases[19]. Alternatively, whether longitudinal reduction in mean arterial pressure was related to changes in CSF biomarkers of AD in a group of cognitively healthy elderly with and without hypertension have been investigated and suggest that hypertensive group may be sensitive to BP reductions [13].

The aim of this review is to see if there are certain similarities in biomarkers-proteins expression in the CSF in AD and SHR and to distinguish whether changes in the expression of proteins in CSF are due to the pathology of the disease or are caused by an alteration in the BCSFB and or CP.

Blood to CSF barrier in AD and SHR

Altered basement membranes (BM) in the BCSFB in AD have been reported by several authors. The thickness of BM in CP was assessed by measuring collagen-IV[10]. Significantly accumulated collagen-IV in BM of CP in 3xTg-AD mice reported for the first time [17]. The exact reason for increased collagen-IV and subsequent thickening of the BMs in AD, at both the capillary and epithelial BMs, needs full characterization. BM thickening reduces permeability [35] and makes plasma ultrafiltration, CP epithelial oxygenation and CSF formation all less efficient. This idea fits the findings of lower expression of AQP-1 and TTR in CP in 3xTg-AD mice [17].

Some authors have reported that chronic hypertension in SHR may cause more pronounced defects in the integrity of the BCSFB than in blood brain barrier (BBB) [2,3]. Transthyretin is a protein involved in the transport of thyroid hormones in the blood and CSF and is present as a 14 kDa monomer (TTRm), as a regulator of 28kDa and as a tetramer of 55kDa in blood and CSF. Transthyretin is found in CP and the subcommissural organ (SCO) cells, and as a soluble monomer in the CSF, and when there are alterations in blood to cerebrospinal fluid barrier (BCSFB) TTRm enters the vascular space and is increased in blood [2,3,15,25]. Therefore, this protein can be used to analyze the integrity of the blood to BCSFB, TTRm, was reduced in hypertensive CSF meaning a change in BCSFB integrity [15,16,18].

Acute phase inflammatory process

Transferrin is a blood plasma glycoprotein for iron ion delivery that binds iron very well, but reversibly. Transferrin has a molecular weight of about 80 kDa and contains two specific high-affinity Fe binding sites. Transferrin is decreased in AD compared with control (Table 1) [7,27,28,33], transferrin is also decreased in our hypertensive rats with respect to WKY [9].

α-2-HS-glycoprotein, is a 46 kDa human plasma protein with extensive polymorphism by isoelectric focusing. The two common alleles are found in all population groups, which have been used as genetic markers in forensic chemogenetics, α-1βglycoprotein and α-2-HS-glycoproteinand are decreased in the CSF of AD with respect to control but the vitamin D carrier is augmented in AD [37,38], in agreement with AD results the α-1-β-glycoprotein and α-2-HS-glycoprotein is also lower in the CSF of SHR and the vitamin D carrier is augmented in the CSF of SHR [16] (Table1).

Majorensis
ISSN 1697-5529

Table 1: Comparison between protein variations in SHR vs WKY and in AD vs Control described in the bibliography.

ID	Protein	SHR vs WKY	AD vs Control
1	α-1-Antitripsin	↑	↑
2	Apolipoprotein A1	↑	↓
3	Apolipoprotein E	↓	↓
4	Transthyretin	↓	↓
5	Albumin	↑	↑
6	α-2-HS Glycoprotein	↓	↓
7	Transferrin	↓	↓
8	α-1-β Glycoprotein	↓	↓
9	Ig gamma-2A chain C region	↑	↑
10	Kininogen	↓	↓
11	Vitamin D Binding Protein	↑	↑
12	Haptoglobin	↑	↑

Two isoforms of α-1-antitrypsin and the heavy chain of immunoglobulin G (IgG), which are proteins used to study the development of AD, are increased in CSF of AD compared to the control (Table 1) [9,12,22,23], both the two α-1-antitrypsin isoforms and the heavy chain of immunoglobulin G (IgG) are also increased in the CSF of SHRs when compared to the CSF of the control [16].

Kininogens are proteins that are defined by their role as precursors of quinine, but they may also have additional functions. The two main types are: high molecular weight kininogen, which is produced by the liver together with prekallikrein and mainly acts as a cofactorin coagulation and inflammation, and has no intrinsic catalytic activity; and the low molecular weight kininogen, which is produced locally by many tissues and is secreted together with tissue kallikrein, kininogen are decreased in the CSF of AD when compared to the CSF of the control [1,8,21,27], and kininogen are also low in the CSF of SHR [16]. Albumin [6,22,33] and haptoglobin [1,11,23,34] are described as high in the CSF in AD and both albumin and haptoglobin are elevated in SHR.

Conclusions

AD patients and SHR showed an important number of proteins variation in CSF (Table 1). The most noteworthy are: α-1 antitrypsin, Apo A1, Apo E, TTR, albumin, α-2-HS glycoprotein, transferrin, α-1-β glycoprotein, IgG, kininogen, vitamin D-binding protein and haptoglobin, which are altered in the same way in CSF of AD than in SHR CSF, except of Apo A1 that was decreased in CSF in AD and increased SHR.

These CSF protein variations could be caused by a disruption or alteration of the BCSFB in AD and HBP. Therefore, we could conclude that AD and HBP in SHR show similarities in CSF protein variations, this fact should be taken into account in order to accurate diagnostic differentiation between AD and the other diseases.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgements

This work was supported by the Fundación Canaria Instituto de Investigación y Ciencias de Puerto del Rosario (INIPRO) projects: nº 01/10 and nº02/10.

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ISSN 1697-5529

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