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Relationship between Cognition, levels of PTX-3, MBL and their polymorphisms: A systematic review

Relação entre cognição, níveis de PTX-3, MBL e seus polimorfismos: uma revisão sistemática

Relación entre cognición, niveles de PTX-3, MBL y sus polimorfismos: una revisión sistemática

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Abstract

Introduction: Studies have suggested that pentraxin 3 (PTX3) and Mannose Binding Lectin (MBL) may interfere with cognitive processes. **Objective:** Identify data reported in the literature involving cognition, PTX3 and MBL. **Materials and Methods:** The research was done in five databases and the selection of studies was performed in two stages. The first involved review of titles and abstracts. Then the full articles were read and those that did not meet the eligibility criteria were excluded. **Results:** A total of 3,097 titles and abstracts were selected, but 3,089 were excluded. Finally, 8 articles were included in the review. The articles pointed out that high levels of PTX-3 could be predictors of cognitive impairment while high levels of MBL could have a protective effect on cognition. **Conclusion:** The current studies are still contradictory and inconclusive, but they lead us to reflect on possible genetic influences of innate immunity in the Central Nervous System. Further research involving the effects of PTX-3 and MBL and its variants on cognition are necessary.

Keywords: Cognition; Genotype; Immunity; Polymorphism, Single Nucleotide; Central Nervous System; Cognition Disorders.

Resumo

Introdução: Estudos têm sugerido que a pentraxina 3 (PTX3) e a Lectina de Ligação a Manose (MBL) podem interferir nos processos cognitivos. **Objetivo:** Identificar dados relatados na literatura envolvendo cognição, PTX3 e MBL. **Materiais e Métodos:** A pesquisa foi realizada em cinco bases de dados e a seleção dos estudos foi realizada em duas etapas. O

primeiro envolveu revisão de títulos e resumos. Em seguida, os artigos completos foram lidos e aqueles que não atenderam aos critérios de elegibilidade foram excluídos. **Resultados:** Foram selecionados 3.097 títulos e resumos, mas 3.089 foram excluídos. Por fim, 8 artigos foram incluídos na revisão. Os artigos apontaram que altos níveis de PTX-3 podem ser preditores de comprometimento cognitivo, enquanto altos níveis de MBL podem ter um efeito protetor sobre a cognição. **Conclusão:** Os estudos atuais ainda são contraditórios e inconclusivos, mas nos levam a refletir sobre as possíveis influências genéticas da imunidade inata no Sistema Nervoso Central. Mais pesquisas envolvendo os efeitos da PTX-3 e MBL e suas variantes na cognição são necessárias.

Palavras-chave: Cognição; Genótipo; Imunidade; Polimorfismo de Nucleotídeo Único; Sistema Nervoso Central; Transtornos Cognitivos.

Resumen

Introducción: Los estudios han sugerido que la pentraxina 3 (PTX3) y la lectina de unión a manosa (MBL) pueden interferir con los procesos cognitivos. **Objetivo:** Identificar los datos reportados en la literatura relacionados con la cognición, PTX3 y MBL. **Materiales y métodos:** La investigación se realizó en cinco bases de datos y la selección de estudios se realizó en dos etapas. La primera implicó la revisión de títulos y resúmenes. Luego se leyeron los artículos completos y se excluyeron aquellos que no cumplían con los criterios de elegibilidad. **Resultados:** Se seleccionaron un total de 3.097 títulos y resúmenes, pero se excluyeron 3.089. Finalmente, se incluyeron 8 artículos en la revisión. Los artículos señalaron que los niveles altos de PTX-3 podrían ser predictores de deterioro cognitivo, mientras que los niveles altos de MBL podrían tener un efecto protector sobre la cognición. **Conclusión:** Los estudios actuales siguen siendo contradictorios y no concluyentes, pero nos llevan a reflexionar sobre posibles influencias genéticas de la inmunidad innata en el Sistema Nervioso Central. Se necesitan más investigaciones que involucren los efectos de PTX-3 y MBL y sus variantes en la cognición.

Palabras clave: Cognición; Genotipo; Inmunidad; Polimorfismo de Nucleótido Simple; Sistema Nervioso Central; Trastornos de la cognición.

1. Introduction

Cognition is characterized as the ability of the human being to assimilate and process the information received from different means, so that they can be converted in to knowledge (Nijstad et al., 2010). It has different domains like perception, attention, learning, memory and decision-making. It is possible to affirm that the exposure of an individual to different situations and environments that can stimulate the use of such domains is a beneficial factor, with respect to the improvement and maintenance of cognition (Holtzer et al., 2007; Shatil 2013). With the advancement of the age, the cerebral morphology and functionality undergo to changes, causing the cognitive processes of the individuals to present a decrease in the performance (Boos et al., 2005; Hedden, 2007). In addition to environmental factors, genetic characteristics of people also seem to influence cognition (Mukamel et al., 2011; Najmabadi et al., 2011; Konopka et al., 2009).

In a clinical study with hypertensive elderly, Yano et al. (2010) suggested that pentraxin 3 (PTX-3) might act as a potential predictor of cognitive impairment. Another study conducted by Chi et al. (2016) showed a strong association between high PTX-3 levels and deficits in psychomotor speed when compared to other inflammatory biomarkers such as SAP (Serum Amyloid P), RAGE (Receptor for Advanced Glycation End product), IL-6 (Interleukin-6), IL-10 (Interleukin-10) and Adiponectin, for example. This protein is used as a rapid marker for local primary activation of innate immunity and inflammation, as well as interacting with extracellular matrix components and participating in tissue remodeling (Carmo et al., 2016; Fossati et al., 2019). In addition, high levels of PTX-3 have been linked to various pathological conditions, severity and infection of the disease (Muller et al., 2001; He et al., 2007).

The PTX-3 protein is secreted by the choroid plexus and astrocytes in the central nervous system of mice (Thouvenot et al., 2006). In humans, PTX-3 is produced and released by phagocytes (such as macrophages, neutrophils and dendritic cells) and non-immune cells at sites of injury or inflammation (in response, for example, to IL-1b and TNF-alpha). In addition, astrocyte derived PTX-3 induces the formation of functional synapses. Primary inflammatory signs, epilepsy or stroke induce increased expression of PTX-3 in brain tissue. The gene encoding the PTX-3 protein (*PTX3*) is located on chromosome 3 and is organized in three exons and two introns (Carmo et al., 2016; Fossati et al., 2019). The PTX-3 protein also interacts with the lectin pathway, such as Mannose Binding Lectin (MBL), promoting the recruitment of molecules on the surface of microorganisms (bacteria, parasites and viruses)

and amplifying the innate response mediated by the complement system, as well as opsonization and phagocytosis (Arora et al., 2001; Jack et al., 2001; Inforzato et al., 2013).

Some studies have shown that the presence of the *MBL2*-OO genotype is associated with: the progression of cognitive dysfunction in adults with HIV after twelve months of observation (Spector et al., 2010), with the fastest progression of HIV-1 and central nervous system (CNS) involvement, predominantly in children under 2 years (Singh et al., 2008) and with an increased risk of adverse neurological outcomes in preterm infants observed for 24 months (Auriti et al., 2014). The presence of *MBL2*-OO genotypes results in lower expression of MBL protein and may lead to impaired innate immunity, opsonic defects, and increased risk for various inherited immunodeficiencies, autoimmunity and severe infectious diseases (Spector et al., 2010; Singh et al., 2008).

Therefore, the objective of this systematic review was to identify whether there are studies that can contribute to a better understanding of the relationship between cognition, serum levels of PTX-3 and MBL, as well as their polymorphisms.

2. Methodology

2.1. Databases and Selection Criteria

At the beginning of February 2020, an electronic search of journals (without time limit) was carried out in the databases: LILACS, MEDLINE, PubMed, SciELO and ScienceDirect. The following descriptors were used in double and triple combinations: Cognition; Cognition Disorders; Pentraxin 3; *PTX3*; Mannose-binding lectin 2; *MBL2*; Single Nucleotide Polymorphism.

Inclusion criteria were articles in Portuguese, English and Spanish; studies involving cognition and *PTX3*; studies involving cognition and *MBL-2*. Review articles or systematic reviews and studies in non-humans were excluded.

2.2. Stages of study selection

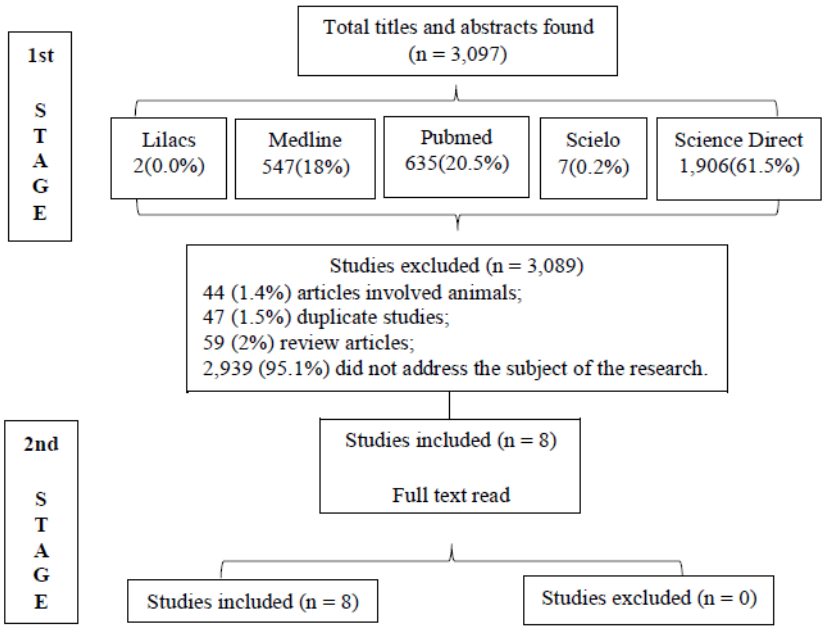
The construction of this systematic review was carried out in two stages. In the first, three members of the research carried out the searches of the articles in the databases combining the descriptors and recording the findings. At this stage, titles and abstracts that did not meet the eligibility criteria were analyzed and eliminated, and the reasons for non-selection were recorded. In the second stage, the complete reading of the previously selected

articles was done and those that did not meet the criteria were eliminated. The data of the articles were extracted and filled in the spreadsheet that contained: Identification of the study (authors), Objective, Characterization of the Sample, Methodology (Biomarkers and cognitive tests examined; Laboratory, statistical and others analysis performed) and Main results (Biomarker - PTX-3 or MBL or their polymorphisms - and cognition; Other considerations). This study was elaborated following the norms and guidelines of the PRISMA platform (Moher et al., 2009).

3. Results

A total of 3,097 titles and abstracts were found in the first moment and then 3,089 were excluded because they did not meet the eligibility criteria or were duplicated. The flowchart in Figure 1 illustrates the steps taken to select studies for review.

Figure 1 Flowchart illustrating research and selection of studies on cognition and PTX-3, MBL or their polymorphisms**.**



Source: Authors.

In Table 1 it is possible to observe the combination of the search terms used in the first stage. Already in Table 2, the main data of the five articles included in this systematic review are identified.

Table 1. Results from the first moment of the systematic review.

Combination of search terms	Total titles and abstracts found			Total excluded
	English	Portuguese	Spanish	
[Cognition and pentraxin 3 and single nucleotide polymorphism]	6	0	0	6
[Cognition and PTX3 and single nucleotide polymorphism]	2	0	0	2
[Cognition and mannose-binding lectin 2 and single nucleotide polymorphism]	3	0	0	3
[Cognition and MBL2 and single nucleotide polymorphism]	4	0	0	4
[Cognition disorders and pentraxin 3 and single nucleotide polymorphism]	4	0	0	4
[Cognition disorders and PTX3 and single nucleotide polymorphism]	2	0	0	2
[Cognition disorders and mannose-binding lectin 2 and single nucleotide polymorphism]	2	0	0	2
[Cognition disorders and MBL2 and single núcleotide polymorphism]	3	0	0	3
[Cognition and pentraxin 3]	52	0	0	48
[Cognition and PTX3]	35	0	0	35
[Cognition and mannose-binding lectin 2]	42	0	0	39
[Cognition and MBL2]	9	0	0	8
[Cognition disorders and pentraxin 3]	35	0	0	35
[Cognition disorders and PTX3]	18	0	0	18
[Cognition disorders and mannose-binding lectin 2]	15	0	0	15
[Cognition disorders and MBL2]	6	0	0	6
[Cognition and single nucleotide polymorphism]	1,235	0	0	1,235
[Cognition disorders and single nucleotide polymorphism]	862	0	0	862
[Pentraxin 3 and single nucleotide polymorphism]	132	0	0	132
[PTX3 and single nucleotide polymorphism]	92	0	0	92
[Mannose-binding lectin 2 and single nucleotide polymorphism]	349	0	0	349
[MBL2 and single nucleotide polymorphism]	189	0	0	189

Source: Research data, 2020.

Table 2. Data from studies included in the systematic review.

Identification	Objective	Characterization of the sample	Methodology		Main results	
			Biomarkers and cognitive tests examined	Laboratory, statistical and others analysis performed	Biomarker (PTX3 or MBL or their polymorphisms) and cognition	Other considerations
Dufek et al. (2009)	To assess whether there are measurable changes in serum inflammatory biomarkers in PD patients and whether the levels of these biomarkers are related to the severity of clinical PD signs.	A group of 29 consecutive idiopathic PD patients from a Movement Disorders Center composed the study cohort.	**Biomarkers:** C-reactive protein, serum amyloid A, alpha 1-antitrypsin, orosomucoid, ceruloplasmin, alpha 2-macroglobulin, transferrin, prealbumin, C3, C4, C1-INH, C1q, MBL, IL-6 and TNF-alfa. **Tests:** MMSE, the Verbal Fluency Test and two subtests of the WMS III – Word Lists I and II.	MBL was assessed by ELISA. The levels of inflammatory biomarkers were determined by means of commercially available diagnostic kits. Reference values were obtained by measuring the concentration of these biomarkers in serum from healthy blood donors. Multivariate regression analysis (ANOVA) was used for the statistical evaluation of the correlation between the severity of PD (as expressed by UPDRS score), MMSE, WMS III, VFT and laboratory immunological parameters.	A reduction in serum MBL was observed in 6 (20.7%) patients (median 0.049, range: 0.037–0.093; normal range: 0.3–3.5 mg/l). No statistically significant correlation was found between the patient's clinical state (neuropsychologic and motor, as expressed by UPDRS III, Hoehn–Yahr, and MMSE) and the immunomarker changes	Patients with clinical signs of vascular parkinsonism or other unrelated brain pathology and with severe cognitive impairment who would be unable to undergo reliable psychological tests were excluded. All patients were taking antiparkinsonian drug therapy. Individuals had a mean age of 68.2 ± 5.4; 9.3 ± 4.4 years of disease duration; 21 were men.
Heyer et al. (2013)	To delineate the role of the complement cascade by analyzing the *C5*, *CFH*, and *MBL2* SNPs of the complement cascade and evaluating their utility in the prediction of CD after CEA.	A nested cohort study of 252 patients prospectively recruited in this IRB-approved study, who consented of the genetic testing. A second group of 155 age and education-matched patients undergoing lumbar	**Biomarkers:** *C5* rs17611, *CFH* rs1061170 and *MBL2* rs7096206 SNPs. **Tests:** Trail Making Test A and B, COWAT, Rey Complex Figure test	PCR products were treated with QIAquick PCR purification kits. Sequencing was performed using the respective primers in conjunction with BigDye Termination v3.1 cycle sequencing kits. SNPs of interest were determined using Chromas 2.01 software.	In the *MBL2* allele, the G/G genotype group differed from the other 2 genotype groups in age (mean age in the G/G group 68.9 ± 5.3 years with 5.0% of patients over 75 years of age; while that in the combined group C/C and G/C, the mean age was 70.4 ± 9.2 years, with 29.8% over 75 years of age) and statin use (50.0% in the G/G group vs 75.2% in the other two groups). Patients with the G/G *MBL2* genotype	All patients were native English speakers with no history of drug abuse, Axis I psychiatric disorders, or previous ipsilateral CEA. No patient received blood transfusion.

		laminectomy or microdiscectomy were contemporaneously recruited to serve as a postoperative reference group for neuropsychometric testing.	(copy) *All patients were examined with the tests preoperatively and postoperatively at 1 day and 1 month after CEA.	Allele and genotype frequencies were compared with values predicted by Hardy-Weinberg equilibrium using a chi-square test. For univariate analyses, the Student t-test, the Wilcoxon rank-sum test, the Fisher exact test, the Pearson chi-square test, and simple logistic regression were used where appropriate. Multiple logistic regression models were constructed to identify independent predictors of CD at 1 day and 1 month after CEA. All factors with $p < 0.20$ in a simple univariate logistic regression were entered into the final models for 1 day and 1 month after CEA. Significance was set at $p \leq 0.05$.	had a 45.0% incidence of CD. There were no significant differences in the incidence of CD at 1 month after CEA in the genotypes of the *MBL2*.	
Lee et al. (2011)	To compare the plasma levels of pentraxin 3 in healthy subjects and patients with neurodegenerative disorders such as mild cognitive impairment, Alzheimer's disease, and Parkinson's disease.	221 Participants were recruited from patients who visited the AD & PD Clinic of Kyungpook National University Hospital (41 normal subjects, 39 MCI, 75 AD and 66 PD).	**Biomarker:** PTX-3 **Tests:** CDR, MMSE	PTX-3 levels in the plasma samples were measured using a commercially available Sandwich ELISA Duo-set. Comparison of PTX-3 levels in the plasma in the control, MCI, AD, and PD groups was done with Tukey's honestly significant difference test for post hoc comparisons. Clinical data were added as predictors, and age, sex, body mass index, years of education, and comorbidities were added as covariates in the ANCOVA models. The categorical data were compared by the chi-square test. ROC curve analysis was done for the PTX-3 levels in the controls versus the PD patients. Spearman's analyses for correlations were also conducted on a subset of participants with all the available data on the relationship between PTX-3 level and MMSE, CDR, and UPDRS scores using linear regression analysis for the covariates. $p < 0.05$ was deemed statistically significant.	PTX-3 levels were increased in PD patients (10.78 ± 8.31 pg/mg protein in plasma) compared with the control subjects (7.10 ± 2.83 pg/mg), the MCI patients (7.65 ± 4.17 pg/mg) and AD patients (7.86 ± 7.39 pg/mg). Statistically significant differences in plasma PTX-3 levels were found between the PD patients and the other 3 groups after adjustment for age, sex, and comorbidities: control versus PD, $p = 0.003$; MCI versus PD, $p = 0.010$; AD versus PD, $p = 0.0001$. No significant correlation was found between plasma PTX-3 levels and MMSE scores (r = 0.094, $p = 0.462$) and CDR scores (r = 0.004, $p = 0.977$) in the PD patients. There was a significant correlation between higher plasma PTX-3 levels and greater dependency on the UPDRS II (ADLs) and the UPDRS III (motor function), which increased with the severity of PD (r = 0.368, $p = 0.003$	The controls had a mean age of 64.73 ± 7 years; Individuals with MCI 69.02 ± 6.93; with AD 72.34 ± 7.09; with PD 65.77 ± 8.88; as for years of schooling, 10.23 ± 3.97; 8.57 ± 5.25; 3.96 ± 3.45; 7.45 ± 4.26 respectively.

					and r = 0.358, *p* = 0.004, respectively).	
				Disease comorbidity was assessed by a modified version of the Charlson Index of Comorbidity. Cerebral magnetic resonance images were also taken.		
Miller et al. (2019)	To evaluate the relationship between PTX-3 and cognitive function	1,547 Participants were recruited from CHS (prospective cohort study designed to examine risk factors for CVD)	**Biomarkers:** PTX-3 **Tests:** 3MSE**,** DSST	Serum PTX-3 was measured in baseline blood samples using PTX3 (human) Detection Set from Alexis Biochemicals; the assay coefficient of variation is 10.2%.	Women had higher baseline scores in 3MSE and DSST compared to men.	Individuals had a mean age of 72.1 ± 0.17; 980 were women.
				Student's *t* tests and pairwise chi-squared tests were used to evaluate differences in baseline characteristics between men and women. Stratified analyses by sex or APOE4 and Cox proportional hazards regression, to evaluate time to incident cognitive impairment, were made.	There was no evidence of effect modification in the longitudinal relationship between serum PTX-3 levels and cognitive decline by APOE4 for 3MSE or DSST (β: −0.10, 95% CI: −0.41, 0.21, *p*=0.54 and β: 0.08, 95% CI: −0.14, 0.30, *p*=0.49, respectively). There was a significant longitudinal association between ln PTX-3 and 3MSE for the unadjusted and adjusted models in women (higher levels of PTX-3 were significantly associated with a faster decline in cognitive function scores in this group).	Participants with a history of CVD events at baseline were excluded.
Sharma et al. (2016)	To examine the association between inflammatory biomarkers and global cognitive function	Subgroup randomly selected of the GEMS (1,046 people free of dementia until the end of the study, 523 diagnosed with dementia incident during follow-up, a sample of 995 participants who provided genetic consent and had sufficient deoxyribonucleic acid for analyzes).	**Biomarkers:** IL-2, IL-6, IL-10, PTX-3, SAP, RAGE, ET-1, PAI-1, adiponectin and resistin. **Test:** 3MSE * Interactions between APOE, age and time were	Laboratory analyses were conducted using multiplex panel technology and an enzyme-linked immunosorbent assay. Plasma biomarkers were tested using stored blood samples collected at baseline. Associations between biomarkers and 3MSE scores were analyzed using Cox regression and mixed-model regression. Bonferroni correction was used to determine	Individuals who experienced a decline in 3MSE score of 5 points or more at any time during follow-up were more likely to be older (79.4 vs 78.6), nonwhite (6.8% vs 3.4%), male (56.6% vs 53.2%), nondrinkers (59.1% vs 56.4%); have lower education (14.8% vs 10.0% did not complete high school); and have MCI at baseline (27% vs 16%). In persons with MCI at baseline, PTX-3 tended to be negatively associated with 3MSE score.	Individuals in the subcohort: 95% white, highly educated and had a mean age of 79.0 ± 3.4. Comorbidities: 55% diagnosed with hypertension and 35% having a history of heart disease.

			also assessed.	significance threshold (p< 0.0025).	PTX-3 was also associated with an increase in the rate of 3MSE decline in those free of MCI at baseline (-0.1, 95% CI = -0.18 to -0.03, p=0.007).	
Singh et al. (2008)	To evaluate the effects of *MBL2* alleles on HIV-1 disease progression and CNS impairment in children.	A cohort of 1037 HIV-1-infected children enrolled in Pediatrics AIDS Clinical Trial Group protocols P152 (n=448) and P300 (n=589)	**Biomarkers:** *MBL2* **Tests:** Mental Developmental Index of Bayley scales, the General Cognitive Index of the McCarthy scales, and the full-scale IQ of the WISC-R or WAIS-R	*MBL2* genotyping was done by means of real-time PCR with melting curve analysis The cross-tabulations of *MBL2* genotypes / haplotypes by race / ethnicity and age groups were used to evaluate the genotype and allele frequencies.	When compared to Hispanic or non-Hispanic whites, non-Hispanic blacks had a higher incidence of genotypes LL and QQ, a higher frequency of AC (p<0.001) and LYPA haplotype, in addition to exclusivity in the CC genotype. The homozygous YY genotype was the most common. Children with the OO genotype showed more rapid CNS impairment than those with either the AA or AO genotypes ($RH_{O/O \text{ vs } (A/O+A/A)}$, 2.15; 95% CI, 1.00-4.64; p = 0.045). Children younger than 2 years with PQ or QQ genotypes underwent more rapid CNS impairment compared with those with the wild-type PP genotype ($RH_{P/Q \text{ vs } P/P}$, 1.73; 95% CI, 1.03-2.91; p = 0.037; $RH_{Q/Q \text{ vs } P/P}$, 1.40; 95% CI, 1.01-1.93; p = 0.042).	Individuals had a median age of 2.3 years; 568 were girls.
Spector et al. (2010)	To examine associations of host genetic variants and neurocognitive impairment in Chinese subjects infected through contaminated blood products.	201 HIV-infected subjects from Anhui, China had neuropsychological tests at baseline and 12 months.	**Biomarkers:** *APOE* ε2, ε3 and ε4 alleles, *MBL2*-AO, *CCR5*-wt/Δ32, *CCR5*-59029-GA, *CCR2-180*-GA, *SDF-1*-GA, *IL4*-589-CT, *MCP-1*-2518-AG, *CX3CR1*-745-GA, -849-CT polymorphisms and *CCL3L1* copy number variants	DNA was genotyped for using real-time PCR. For bivariate analyses, categorical variables were compared using either the Chi square test or the Fisher's exact test. Continuous variables were compared using the Student's t test for parametric data or the Mann-Whitney U test for non-parametric data. *p*-	At baseline, no significant differences in rates of cognitive impairment were observed for study subjects with different *MBL*2 genotypes. By the end of 12 months of follow-up, 41%, 43% and 60% of subjects were impaired in the AA, AO and OO groups, respectively. This association held in multivariate analyses controlling for CD4+ lymphocyte count, viral load or both at baseline (p< 0.006 for each).	60.7% were male with a mean schooling of 5.5 years. AIDS was diagnosed in 113 subjects at baseline and 114 were receiving antiretroviral therapy. The mean CD4+ lymphocyte count at baseline was 349/mm3 which increased to 400/mm3 at 12 months.

			Tests: Color Trails I and II, WCST, Category Test, Animal fluency, Action fluency, PASAT-50, WMS-III Spatial Span, HVLT-R Learning, BVMT-R Learning, Grooved Pegboard DH and NDH, WAIS-III Digit Symbol, Trail Making Test A, Stroop color.	values were considered significant if <0.05 two-tailed.		The plasma HIV-1 RNA was detectable in 127 subjects at baseline with the mean viral load of 4.09 log10 copies/mL.
Yano et al. (2010)	To examine the association between inflammatory biomarkers and cognitive function, to determine the best biomarker of cognitive impairment and whether there is a significant interaction between these inflammatory biomarkers and the 24-hour blood pressure level.	A cross-sectional study with 210 patients with essential hypertension, who lived independently and were not nursing home residents.	**Biomarkers:** PTX-3, hs-CRP levels **Test:** MMSE	Plasma PTX-3 was measured by a commercially available enzyme-linked immunosorbent assay kit. The intra-assay and interassay variation coefficients of each test were both less than 7%. All measurements were performed within 6 months. All patients underwent measurement of BMI, waist circumference at the umbilical portion and 24-hour BP level. The carotid arteries were examined bilaterally at the level of the CCA, the bulb, and the internal carotid artery, as measured from both transverse and longitudinal orientations Associations between the individual parameters were calculated using Spearman's correlation method. To assess independent associations between the PTX-3 or hs-CRP levels and the MMSE score, we used a stepwise multivariable linear regression analysis (p< 0.05).	There was no significant association between the PTX-3 and hs-CRP levels themselves (r=−0.077; p=0.266). The PTX-3 level was significantly inversely associated with obesity, hypertriglycemia and with the % BW change over the past 5 years. The PTX-3 level was weakly, but significantly associated with the CCA-IMT level. None of the medications, including antihypertensive drugs and statins, were associated with either the PTX-3 levels. When the comparisons were restricted to nonobese subjects (BMI < 25kg/m2, n = 119), the PTX-3 levels remained significantly associated with the MMSE score (r = −0.239, p< 0.01). A stepwise multivariate regression analysis showed that the PTX-3 level was significantly associated with the MMSE score as also	Individuals had a mean age of 74.4 ± 6.9; 8.5 ± 1.5 years of schooling; 44% were men. There were five patients with a previous history of CAD and one patient with a previous history of heart failure.

between the PTX-3 level and 24-hour systolic BP (SBP) level in determining the MMSE score independently of age, sex, BMI, smoking status, education level, a previous history of cardiovascular disease, and renal function.

AD, Alzheimer's Disease; **ADLs**, Activities of Daily Living; **AIDS**, Acquired Immunodeficiency Syndrome; **ANCOVA**, Analysis of the Covariance; **APOE**, apolipoprotein E; **BMI**, body mass index; **BP**, Blood Pressure; **BW**, Body Weight; **C5**, Complement Component 5; **CAD**, Coronary Arterial Disease; **CCA**, Common Carotid Artery; **CD**, cognitive dysfunction; **CDR**, Clinical Dementia Rating; **CEA**, carotid endarterectomy; **CFH**, Complement Factor H; **CHS**, Cardiovascular Health Study; **CNS**, Central Nervous System; **COWAT**, Controlled Oral Word Association Test; **CVD**, Cardiovascular Diseases; **DSST**, Digit Symbol Substitution Test; **ET-1**, Endothelin-1; **GDS**, Global Deficit Score; **GEMS**, Ginkgo Evaluation of Memory Study; **HIV**, Human Immunodeficiency Virus; **Hs-CRP**, High-Sensitivity C-Reactive Protein; **IL-2**, Interleukin-2; **IL-6**, Interleukin-6; **IL-10**, Interleukin-10; **IMT**, Intima-Media Thickness; **MBL**, Mannose-Binding Lectin; **MBL2**, Mannose-Binding Lectin 2; **MCI**, Mild Cognitive Impairment; **MMSE**, Mini-Mental State Examination; **3MSE**, modified Mini-Mental State Examination; **PAI-1**, Plasminogen Activator Inhibitor-1; **PCR**, Polymerase Chain Reaction; **PD**, Parkinson's disease; **PTX3**, Pentraxin 3; **RAGE**, Receptor for Advanced Glycation End product; **RH**, Relative Hazard; **ROC**, Receiver Operating Characteristic; **SAP**, Serum Amyloid P; **SBP**, Systolic Blood Pressure; **SNPs**, Polymorphisms; **UPDRS**, Unified Parkinson's Disease Rating Scale; **VFT**, Verbal Fluency Test; **WAIS-R,** Wechsler Adult Intelligence Scale: Revised; **WISC-R,** Wechsler Intelligence Scale for Children: Revised; **WMS III,** Wechsler Memory Scale, third edition. Source: Research data, 2020.

A number of limitations were listed by the authors of the studies that met the eligibility criteria. These included the following: fragility of the test applied to evaluate cognitive functions, participants with comorbidities that could interfere with the results, small size samples (Sharma et al., 2016); No causal relationship could be inferred as a cross-sectional study, blood samples inadequately stored (-40°C, which may alter PTX-3 concentration by protein degradation) (Yano et al., 2010); The selection bias may have occurred because the participants were from the same establishment or due to institutional standards of the surgical or anesthetic technique used (Heyer et al., 2013); The results were not adjusted for the drugs used, there was a comparison between non-homogeneous diseases (Lee et al., 2011); The time of infection was not established and there was no record of when antiretroviral treatment was initiated, participants were infected through blood products and may not be applicable to persons otherwise infected (Spector et al., 2010); Biomarkers were not measured in a control group – use of normative data (Dufek et al., 2009); PTX-3 was measured only at baseline, making it impossible to assess the relationship between changes in PTX-3 and cognitive function over time; possibility of a learning effect, frequently observed in longitudinal analyzes with repeated measures, underestimating the true cognitive decline through the 3MSE (Miller et al., 2019); The effect of *MBL2* polymorphisms on HIV-1 infection in children cannot be extended to adults due to the different characteristics of these two populations (Singh et al., 2008).

4. Discussion

With increasing longevity of human populations, many researchers try to find a useful biomarker for early detection of cognitive impairment and neurodegenerative diseases (Sharma et al., 2016). It is known that inflammatory processes contribute to many acute and chronic Central Nervous System (CNS) disorders. In the brain, inflammation is initiated by activation of microglia, endothelia, astrocytes, ependymal and meningeal cells, leading to innate immunity (Rajkovic et al., 2016; Zanier et al., 2011)

Acute phase proteins (APP), such as pentraxins, are used as biomarkers of inflammation and potential biomarkers for neurodegeneration (Rajkovic et al., 2016; Osera et al., 2012). Among the long-family pentraxins, PTX-3 has been recognized to play important roles in CNS disorders, having both harmful and neuroprotective effects (Rajkovic et al., 2016).

In this systematic review, four selected articles addressed the plasma levels of PTX-3 and its relations with cognitive alterations evaluated by the Mini-Mental State Examination (MMSE) (Yano et al., 2010; Lee et al., 2011) and by an adapted form of this instrument (Miller et al., 2019; Sharma et al., 2016). Of the four studies, only the studies by Yano et al. (2010) and Miller et al. (2019) showed that high plasma levels of PTX-3 were associated with a cognitive decline in elderly people with hypertension. In the first, the situation was observed in both sexes and in the second, only in women.

The relationship of plasma concentrations of PTX-3 in individuals with cardiovascular risk factors, such as hypertension, has also been demonstrated in other studies. During the inflammatory process, blood vessels produce large amounts of PTX-3, which adversely affects the cardiovascular system. Local and systemic inflammation plays an important role in the development of endothelial dysfunction, thus suggesting a key role for APP (Jylhävä et al., 2011; Fornai et al., 2016; Parlak et al., 2012). Several cell types produce PTX-3, such as vascular endothelial cells, vascular smooth muscle cells, monocytes / macrophages, neurons, and astrocytes. Astrocytic PTX3 can support the integrity of the blood-brain barrier by counteracting the negative effects of vascular endothelial growth factor (VEGF) on it during the acute phase of a stroke, for example. However, it may inhibit brain repair, such as compensatory angiogenesis, after this phase (Shindo et al., 2016).

Osera et al. (2012) and Ko et al. (2012) agree and report in their studies that the amplified inflammatory response of PTX-3 leads to the failure of macrophages to remove apoptotic neurons contributing to the development of Alzheimer's Disease. Already in the study by Lee, Choi & Suk (2011), increased plasma levels of PTX-3 were found in people with Parkinson's disease (PD), when compared with people with Alzheimer’s disease (AD) and mild cognitive impairment (MCI). In addition, there was a significant association with impairment in motor function and greater dependence on daily life activities, not observed in cognitive aspects as mentioned in the two studies above.

Another biomarker that has been investigated for association with cognitive dysfunctions is MBL. In this systematic review, one of the studies (Dufek et al., 2009) discussed cognitive aspects and levels in MBL serum, while three others were identified (Spector et al., 2010; Singh, Lieser et al., 2008; Heyer et al., 2013) addressing these aspects with *MBL2* genotypes. Dufek et al. (2009) did not observe in their research a difference in cognitive aspects between participants with PD with reduced levels of MBL and those with normal levels.

Heyer et al. (2013) evaluated the incidence of cognitive dysfunction after carotid endarterectomy and the *MBL2* genotype. An incidence of 45% of cognitive dysfunction was observed in those with *MBL2* GG genotype 1 day after surgery, with no significant difference in incidence of the deficit, among genotypes, 1 month after the procedure. Differently, in the study by Spector et al. (2010), HIV-infected individuals were evaluated but significant differences in cognitive impairment patterns in the different *MBL2* genotypes were not observed at the beginning. The fact was modified after 12 months, when 60% of the OO group presented the deficit. Similar to the study by Spector et al. (2010), Singh et al. (2008) investigated the effects of *MBL2* on people with HIV and, in their findings, also observed a more rapid disease progression and associated cognitive impairment to the OO genotype of *MBL2*, although this study was with children. MBL deficiency predisposes to infection by microorganisms as viruses, for example, and this impact appears to be more pronounced in immunocompromised patients. It is possible that MBL is also important in determining the host's response to HIV infection. Thus, the virus may be mediating some of its immunosuppressive effects by actions in the pathways mediated by MBL. The association of genetic variants with low and high serum levels of MBL and the increase in the prevalence of HIV infection has been shown, but does not yet present a conclusive result (Eisen et al. 2008).

In the studies cited, we can hypothesize the protective effect of the presence of high levels of MBL on cognitive aspects, since the findings with the GG and OO genotypes were in small samples compared with the other groups in each study.

The limitation of this systematic review is due to few articles found addressing the suggested topic; therefore, it was not possible to conduct an extensive discussion. Further research involving the effects of *PTX3* and *MBL2*, and its variants on cognition, as well as the application of more complex and adequate cognitive instruments to the researched population, are necessary. The current studies are still contradictory and inconclusive, but they lead us to reflect on possible genetic influences in the Central Nervous System, whether harmful or beneficial.

5. Final Considerations

The articles pointed out that high levels of PTX-3 could be predictors of cognitive impairment while high levels of MBL could have a protective effect on cognition. The current studies are still contradictory and inconclusive, but they lead us to reflect on possible genetic

influences of innate immunity in the Central Nervous System. Further research involving the effects of PTX-3 and MBL and its variants on cognition are necessary.

References

Arora, M.; Munoz, E. & Tenner, A.J. (2001). Identification of a site on mannan-binding lectin critical for enhancement of phagocytosis. *J Biol Chem*, 276, 43087-43094. doi:10.1074/jbc.M105455200

Auriti, C.; Prencipe, G.; Caravale, B.; Coletti, M.F.; Ronchetti, M.P.; Piersigilli, F.; Azzari, C. & Di Ciommo, V.M. (2014). MBL2 gene polymorphisms increase the risk of adverse neurological outcome in preterm infants: a preliminary prospective study. *Pediatr Res*, 76(5), 464-469. doi:10.1038/pr.2014.118

Boos, G.L.; Soares, L.F. & Oliveira Filho, G.R. (2005). Postoperative cognitive dysfunction: prevalence and associated factors. *Rev Bras Anestesiol*, 55, 517-524. doi:10.1590/s0034-70942005000500006

Carmo, R.F.; Aroucha, D.; Vasconcelos, L.R.S.; Pereira, L.M.M.B.; Moura, P. & Cavalcanti, M.S.M. (2016). Genetic variation in PTX3 and plasma levels associated with hepatocellular carcinoma in patients with HCV. *J Viral Hepat*, 23, 116–122. doi:10.1111/jvh.12472

Chi, G.C.; Fitzpatrick, A.L.; Sharma, M.; Jenny, N.S.; Lopez, O.L. & DeKosky, S.T. (2016). Inflammatory biomarkers predict domain-specific cognitive decline in older adults. *J Gerontol A Biol Sci Med Sci*, 72, 796-803. doi:10.1093/gerona/glw155

Dufek, M.; Hamanová, M.; Lokaj, J.; Goldemund, D.; Rektorová, I.; Michálková, Z.; Sheardová, K. & Rektor, I. (2009). Serum inflammatory biomarkers in Parkinson's disease, Parkinsonism. *Relat Disord*, 15, 318–320. doi:10.1016/j.parkreldis.2008.05.014

Eisen, S.; Dzwonek, A. & Klein, N.J. (2008). Mannose-Binding Lectin in HIV Infection. *Future Virol*, 3, 225–233. doi:10.2217/17460794.3.3.225

Fornai, F.; Carrizzo, A.; Forte, M.; Ambrosio, M.; Damato, A.; Ferrucci, M.; Biagioni, F.; Busceti, C.; Puca, A.A. & Vecchione, C. (2016). The inflammatory protein Pentraxin 3 in cardiovascular disease. *Immun Ageing*, 13, 25. doi:10.1186/s12979-016-0080-1

Fossati, G.; Pozzi, D.; Canzi, A.; Mirabella, F.; Valentino, S.; Morini, R.; Ghirardini, E.; Filipello, F.; Moretti, M.; Gotti, C.; Annis, D.S.; Mosher, D.F.; Garlanda, C.; Bottazzi, B.; Taraboletti, G.; Mantovani, A.; Matteoli, M. & Menna, E. (2019). Pentraxin 3 regulates synaptic function by inducing AMPA receptor clustering via ECM remodeling and b1-integrin. *Embo J*, 3, 38. doi: 10.15252/embj.201899529

He, X.; Han, B. & Liu, M. (2007). Long pentraxin 3 in pulmonary infection and acute lung injury. *Am J Physiol Lung Cell Mol Physiol*, 292, L1039-L1049. doi:10.1152/ajplung.00490.2006

Hedden, T. (2007). Imaging Cognition in the Aging Human Brain. In Riddle, D.R. (Ed.), *Brain Aging: Models, Methods, and Mechanisms* (pp. 01-38). Boca Raton: CRC Press/Taylor & Francis.

Heyer, E.J.; Kellner, C.P.; Malone, H.R.; Bruce, S.S.; Mergeche, J.L.; Ward, J.T. & Connolly, E.S. Jr. (2013).
Complement polymorphisms and cognitive dysfunction after carotid endarterectomy. *J Neurosurg*, 119, 648-654. doi:10.3171/2013.4.JNS1368

Holtzer, R.; Friedman, R.; Lipton, R.B.; Katz, M.; Xue, X. & Verghese, J. (2007). The relationship between specific cognitive functions and falls in aging. *Neuropsychology*, 21, 540-548. doi:10.1037/0894-4105.21.5.540

Inforzato, A.; Doni, A.; Barajon, I.; Leone, R.; Garlanda, C.; Bottazzi, B. & Mantovani, A. (2013). PTX3 as a paradigm for the interaction of pentraxins with the Complement system. *Semin Immunol*, 25, 79-85. doi:10.1016/j.smim.2013.05.002

Jack, D.L.; Klein, N.J. & Turner, M.W. (2001). Mannose-binding lectin: targeting the microbial world for complement attack and opsonophagocytosis. *Immunol Rev*, 180, 86-99. doi:10.1034/j.1600-065x.2001.1800108.x

Jylhävä, J.; Haarala, A.; Kähönen, M.; Lehtimäki, T.; Jula, A.; Moilanen, L.; Kesäniemi, Y.A.; Nieminen, M.S. & Hurme, M. (2011). Pentraxin 3 (PTX3) is associated with cardiovascular risk factors: the Health 2000 Survey. *Clin Exp Immunol*, 164, 211-217. doi:10.1111/j.1365-2249.2011.04354.x

Ko, C.Y.; Chang, L.H.; Lee, Y.C.; Sterneck, E.; Cheng, C.P.; Chen, S.H.; Huang, A.M.; Tseng, J.T. & Wang, J.M. (2012). CCAAT/enhancer binding protein delta (CEBPD) elevating PTX3 expression inhibits macrophage-mediated phagocytosis of dying neuron cells. *Neurobiol Aging*, 33, 422.e11-25. doi:10.1016/j.neurobiolaging.2010.09.017

Konopka, G.; Bomar, J.M.; Winden, K.; Coppola, G.; Jonsson, Z.O.; Gao, F.; Peng, S.; Preuss, T.M.; Wohlschlegel, J.A. & Geschwind, D.H. (2009). Human-specific transcriptional regulation of CNS development genes by FOXP2. *Nature*, 462 213-217. doi:10.1038/nature08549

Lee, H.W.; Choi, J. & Suk, K. (2011). Increases of pentraxin 3 plasma levels in patients with Parkinson's disease. *Mov Disord*, 26, 2364-2370. doi:10.1002/mds.23871

Miller, L.M.; Jenny, N.S. Rawlings, A.M.; Arnold, A.M.; Fitzpatrick, A.L.; Lopez, O.L. & Odden, M.C. (2019). Sex Differences in the Association Between Pentraxin 3 and Cognitive Decline: The Cardiovascular Health Study. *J Gerontol A Biol Sci Med Sci*, 75(8), 1523-1529. doi:10.1093/gerona/glz217

Moher, D.; Liberati, A.; Tetzlaff, J.; Altman; D.G. & PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PloSMed*, 6(7), 1–6. doi:10.1371/journal.pmed.1000097

Mukamel, Z.; Konopka, G.; Wexler, E.; Osborn, G.E.; Dong, H.; Bergman, M.Y.; Levitt, P. & Geschwind, D.H. (2011). Regulation of MET by FOXP2, genes implicated in higher cognitive dysfunction and autism risk. *J Neurosci*, 31(32), 11437-11442. doi:10.1523/JNEUROSCI.0181-11.2011

Muller, B.; Peri, G.; Doni, A.; Torri, V.; Landmann, R.; Bottazzi, B. & Mantovani, A. (2001). Circulating levels of the long pentraxin PTX3 correlate with severity of infection in critically ill patients. *Crit Care Med*, 29, 1404-1407. doi:10.1097/00003246-200107000-00017

Najmabadi, H.; Hu, H.; Garshasbi, M.; Zemojtel, T.; Abedini, S.S.; Chen, W.; Hosseini, M.; Behjati, F.; Haas, S.; Jamali, P.; Zecha, A.; Mohseni, M.; Püttmann, L.; Vahid, L.N.; Jensen, C.; Moheb, L.A.; Bienek, M.; Larti, F.; Mueller, I.; Weissmann, R.; Darvish, H.; Wrogemann, K.; Hadavi, V.; Lipkowitz, B.; Esmaeeli-Nieh, S.; Wieczorek, D.; Kariminejad, R.; Firouzabadi, S.G.; Cohen, M.; Fattahi, Z.; Rost, I.; Mojahedi, F.; Hertzberg, C.; Dehghan, A.; Rajab, A.; Banavandi, M.J.; Hoffer, J.; Falah, M.; Musante, L.; Kalscheuer, V.; Ullmann, R.; Kuss, A.W.; Tzschach, A.; Kahrizi, K. & Ropers, H.H. (2011). Deep sequencing reveals 50 novel genes for recessive cognitive disorders. *Nature*, 478 (7367), 57-63. doi:10.1038/nature10423

Nijstad, B.A.; De Dreu, C.K.; Rietzschel, E.F. & Baas, M. (2010). The dual pathway to creativity model: Creative ideation as a function of flexibility and persistence. *Eur Rev Soc Psychol*, 21, 34-77. doi:10.1080/10463281003765323

Osera, C.; Pascale, A.; Amadio, M.; Venturini, L.; Govoni, S.; & Ricevuti, G. (2012). Pentraxins and Alzheimer's disease: at the interface between biomarkers and pharmacological targets. *Ageing Res Rev*, 11, 189-198. doi:10.1016/j.arr.2011.12.004

Parlak, A.; Aydogan, U.; Iyisoy, A.; Dikililer, M.A.; Kut, A.; Cakır, E. & Sağlam, K. (2012). Elevated pentraxin-3 levels are related to blood pressure levels in hypertensive patients: an observational study. *Anadolu Kardiyol Derg*, 12(4), 298-304. doi:10.5152/akd.2012.092

Rajkovic, I.; Denes, A.; Allan, S.M. & Pinteaux, E. (2016). Emerging roles of the acute phase protein pentraxin-3 during central nervous system disorders. *J Neuroimmunol*, 292, 27–33. doi:10.1016/j.jneuroim.2015.12.007

Sharma, M.; Fitzpatrick, A.L.; Arnold, A.M.; Chi, G.; Lopez, O.L.; Jenny, N.S. & Dekosky, S.T. (2016). Inflammatory Biomarkers and Cognitive Decline:

The Ginkgo Evaluation of Memory Study. *J Am Geriatr Soc*, 64(6), 1171-1177. doi:10.1111/jgs.14140

Shatil, E. (2013). Does combined cognitive training and physical activity training enhance cognitive abilities more than either alone? A four-condition randomized controlled trial among healthy older adults. *Front aging neurosci*, 26, 8. doi:10.3389/fnagi.2013.00008

Shindo, A.; Maki, T.; Mandeville, E.T.; Liang, A.C.; Egawa, N.; Itoh, K.; Itoh, N.; Borlongan, M.; Holder, J.C.; Chuang, T.T.; McNeish, J.D.; Tomimoto, H.; Lok, J.; Lo, E.H. & Arai, K. (2016). Astrocyte-Derived Pentraxin 3 Supports Blood-Brain Barrier Integrity Under Acute Phase of Stroke. *Stroke*, 47(4), 1094-100. doi: 10.1161/STROKEAHA.115.012133

Singh, K.K.; Lieser, A.; Ruan, P.K.; Fenton, T. & Spector, S.A. (2008). An age-dependent association of mannose-binding lectin-2 genetic variants on HIV-1–related disease in children. *J Allergy Clin Immunol*, 122, 173-180. doi:10.1016/j.jaci.2008.05.025

Spector, S.A.; Singh, K.K.; Gupta, S.; Cystique, L.A.; Jin, H.; Letendre, S.; Schrier, R.; Wu, Z.; Hong, K.X.; Yu, X.; Shi, C.; Heaton, R.K. & HNRC Group. (2010). APOE epsilon4 and MBL-2 O/O Genotypes are Associated with Neurocognitive Impairment in HIV-Infected Plasma Donors from Anhui Province, China. *AIDS*, 24 (10), 1471-1479. doi:10.1097/QAD.0b013e328339e25c

Thouvenot, E.; Lafon-Cazal, M.; Demettre, E.; Jouin, P.; Bockaert, J. & Marin, P. (2006). The proteomic analysis of mouse choroid plexus secretome reveals a high protein secretion capacity of choroidal epithelial cells. *Proteomics*, 6, 5941-5952. doi:10.1002/pmic.200600096

Yano, Y.; Matsuda, S.; Hatakeyama, K.; Sato, Y.; Imamura, T.; Shimada, K.; Kodama, T.; Kario, K. & Asada, Y. (2010). Plasma Pentraxin 3, butnot High-sensitivity C-reactiveProtein, is a Useful Inflammatory Biomarker for Predicting Cognitive Impairment in Elderly Hypertensive Patients. *J Gerontol A Biol Sci Med Sci*, 65, 547-552. doi:10.1093/gerona/glq030

Zanier, E.R.; Brandi, G.; Peri, G.; Longhi, L.; Zoerle, T.; Tettamanti, M.; Garlanda, C.;

Sigurtà, A.; Valaperta, S.; Mantovani, A.; De Simoni, M.G. & Stocchetti, N. (2011). Cerebrospinal fluid pentraxin 3 early after subarachnoid hemorrhage is associated with vasosp asm. *Intensive Care Med*, 37, 302-309. doi:10.1007/s00134-010-2075-2

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