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Psammoma bodies as signs of choroid plexus ageing – a morphometric analysis

Psamomatozna telašca kao pokazatelji starenja horoidnog pleksusa – morfometrijska analiza

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Abstract

Background/Aim. Psammoma bodies (PB) are regarded as benign consequences of ageing in choroid plexus stroma. The aim of this study was to assess the morphometric characteristics of psammoma bodies of all four choroid plexuses during the ageing process. Our intention was to find the possible relations between psammoma bodies and choroid plexus and blood vessels parameters. **Methods**. This study was conducted on the material taken from 15 cadavers during routine autopsies. Tissue samples were collected from both lateral, third and forth ventricles' choroid plexus. Slices were stained with Mallory trichrome stains. In each image, we analyzed morphometrically the epithelium, blood vessels present and all the psammoma bodies. **Results**. With age, right choroid plexus surface density decreases ($p < 0.05$), while the psammoma bodies volume density increases ($p < 0.05$). A decrease in the blood vessels volume density was observed in the third ventricle's choroid plexus ($p < 0.05$), as well as an age-related decrease in the psammoma bodies perimeter ($p < 0.01$). Not associated with ageing, the increase in psammoma bodies perimeter and volume density predicts a decrease in choroid plexus surface density ($p < 0.05$ and $p < 0.001$, respectively). There was a decrease in the volume density of blood vessels with age and with the increase in Feret's diameter of psammoma bodies, ($p < 0.001$ and $p < 0.05$, respectively). **Conclusion**. We want to point out that there is an association between ageing and increased size and volume density of psammoma bodies. More important is the fact that psammoma bodies' presence and their morphometric characteristics are good predictors of changes occurring on the level of choroid plexus structure and vascularization, which may have crucial effects on the choroid plexus physiology.

Key words:
choroid plexus; cell aging; image cytometry; blood vessels.

Apstrakt

Uvod/Cilj. Psamomatozna telašca smatraju se benignom posledicom starenja u stromi horoidnog pleksusa. Cilj rada bio je da se utvrde morfometrijske karakteristike psamomatoznih telašaca u sva četiri horoidna pleksusa, tokom procesa starenja. Osim toga, namera je bila da se pronađe povezanost između parametara psamomatoznih telašaca i parametara horoidnog pleksusa i krvnih sudova. **Metode**. Ova studija urađena je na materijalu uzetom sa 15 kadavera tokom rutinske autopsije. Tkivni uzorci uzimani su sa horoidnih pleksusa iz obe lateralne, treće i četvrte moždane komore. Dobijeni preseci bojeni su Mallory *trichrome* metodom. Na dobijenim slikama, morfometrijski je analiziran epitel, krvni sudovi i sva prisutna psamomatozna telašca. **Rezultati**. Sa starenjem, smanjuje se površinska gustina horoidnog pleksusa ($p < 0.05$), ali raste zapreminska gustina psamomatoznih telašaca ($p < 0.05$). Smanjenje zapreminske gustine krvnih sudova uočeno je u horoidnom pleksusu treće moždane komore ($p < 0.05$), kao i smanjenje perimetra psamomatoznih telašaca ($p < 0.01$). Povećanje perimetra i zapreminske gustine psamomatoznih telašaca daje mogućnost predviđanja pada površinske gustine horoidnog pleksusa ($p < 0.05$ i $p < 0.001$), bez obzira na starost. Sa starenjem i porastom Feretovog dijametra psamomatoznih telašaca, smanjuje se zapreminska gustina krvnih sudova ($p < 0.001$ i $p < 0.05$). **Zaključak**. Možemo istaći da postoji međusobna povezanost između starenja i povećane veličine i zapreminske gustine psamomatoznih telašaca. Što je još važnije, prisustvo psamomatoznih telašaca i njihove morfometrijske karakteristike su dobri prediktori promena na horoidnom pleksusu i u njegovoj vaskularizaciji, što može imate vrlo značajne efekte na fiziologiju horoidnog pleksusa.

Ključne reči:
pleksus, horoidni; ćelija, starenje; morfometrija; krvni sudovi.

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Introduction

Choroid plexus (CP) is a leaf-like structure, highly vascularized with fenestrated capillaries and venules, located within both lateral (LV), the third (V3) and the fourth cerebral ventricle (V4) [1]. The role of CP is complex, beyond simple secretion of cerebrospinal fluid. Its epithelium shows enzymatic activity, transports molecules in both ways acting as a selective blood-brain barrier, and takes a role in immunoreactivity [2]. Besides flattening of the CP epithelium and shortened choroidal villi [3–5], ageing of the CP is characterized with calcification, cyst formation, psammoma bodies (PBs) formation and iron deposition [6]. Cerebral microvasculature changes with age as well, showing an increase in the cross-sectional area of the capillary wall, number and length per unit volume of capillaries, due to endothelium cells elongation, perivascular gliofibrillar proliferation and basement membrane thickness, while the number of endothelial cells decreases [4, 7, 8]. As the result, the main physiologic changes in the aged are decreased cerebrospinal fluid secretion and more than two times diminished clearance of various molecules, endogenous and exogenous, from the central nervous system [5, 9].

Psammoma bodies are regarded as benign consequences of ageing in choroid plexus stroma. On the other hand, they are seen in numerous tumorous formations of other tissues, mostly with papillary structure [10–15], but never in the view of senescence. In malignant tumors PBs are associated with better prognosis (vascular thrombosis, calcification and tumor necrosis) [16], while in the CP, their presence is correlated with epithelium atrophy and, therefore, reduced physiological functioning [17]. Nevertheless, recent studies suggest that in case of thyroid papillary carcinoma, the presence of either intratumorous, or extratumorous PBs, is associated with aggressiveness [12, 18]. There are no definite theories of the PBs formation mechanism, neither in the CP, nor in the other tissues. Even though there is such an extreme difference between the PBs in CP and other tissues, in relation to normal ageing process versus malignant pathologic conditions, some similarities exist: fenestrated capillaries, a characteristic of both the CP and some malignancies associated with the PBs, as a consequence of augmented angiogenesis, ease the entrance of noxious substances, as well as leukocytes [19] or even nanobacteria [20, 21]. A proposed mechanism is that the presence of these agents, or inflammation itself, may induce stromal reaction and the PBs formation [22].

The aim of this study was to assess the morphology and the number of the PBs in the CP during the ageing process. Furthermore, we tested the role of age, sex and the PBs morphology and number in predicting the changes in morphology and structure of the CP of all four cerebral ventricles.

Methods

This study was conducted on the material taken from 15 cadavers, 8 males and 7 females, during routine autopsies performed at the Department of Forensic Medicine, Faculty of Medicine, Niš, Serbia. It was approved by the Ethics Committee of the University of Niš, Faculty of Medicine. Neither of the cadavers included had been previously diagnosed a nervous system disease, nor any abnormalities or brain damage had been observed at the autopsy. Tissue samples were collected from both lateral, third and forth ventricles' CP. Cadavers' age ranged from 35 to 84 years (average 61.8 ± 15.0 years). Tissue obtained was fixated in 10% buffered formalin, and embedded into paraffin blocks. Afterwards, slices, 5 μm thick, were stained with Mallory trichrome stains.

In each case, 10 fields of vision, randomly selected, were analyzed under a light microscope (Leica DM2500) and photographed under the 10x times lens magnification with digital camera (Leica DFC420, resolution 2592 × 1944 pixels) mounted on the third microscope ocular. Morphometric analysis was performed using Image J image processing and analysis software (version 1.49, National Institutes of Health, USA). After spatial calibration using an objective micrometar, in each image, we have analyzed the epithelium and the blood vessels present in order to quantify the surface density of choroid plexus (SDCP), as well as the volume density of the blood vessels (VDBV). Beside counting all the PBs, each was measured giving us the following measures: average total area per case (APB), average perimeter (PPB), average Feret's diameter (FDPB), numeric (NDPB) and volume density of PBs (VDPB). A multipurpose test system M168 (d = 82.0μm, Lt = 6888.1μm, At = 978365.9μm^2) was used for the stereologycal analysis, and the calculation of SDCP, VDBV, NDPB and VDPB [23].

The data analysis was performed by Statistical Package for Social Sciences (SPSS 16.0; Chicago, IL, USA). The normality of the data distribution was tested using a contingent on distributional characteristics (i.e. skewness, kurtoasis, presence of extreme values, Shapiro-Wilk test). Baseline characteristics are presented as means with standard deviation (SDs). Data deviating heavily from normal distribution was displayed as median and interquartile range. A non-parametric methods, Mood's median test for independent samples was used to determine the differences in observed measures between age groups. Univariate linear regression was performed in order to determine the relevance of age, sex and morphometric parameters of PBsin predicting the changes in choroid plexus. A *p*-value less than 0.05 was considered to be a measure of statistical significance.

Results

Histological analysis

Tissue slices obtained represented choroidal villi, as well as the fibrovascular core without or with small sections of the epithelium visible. As it can be seen in Figure 1, numerous amorphous calcifications could be observed in cross and longitudinally sectioned choroidal villi. Psammoma bodies analyzed were present in both forms: immature PBs with amorphous core and mature lamellar PBs. As a result of the ageing process, especially in the old cases, there were cystic formations containing the PBs. Psammoma bodies were not observed in five cases: four samples of the forth

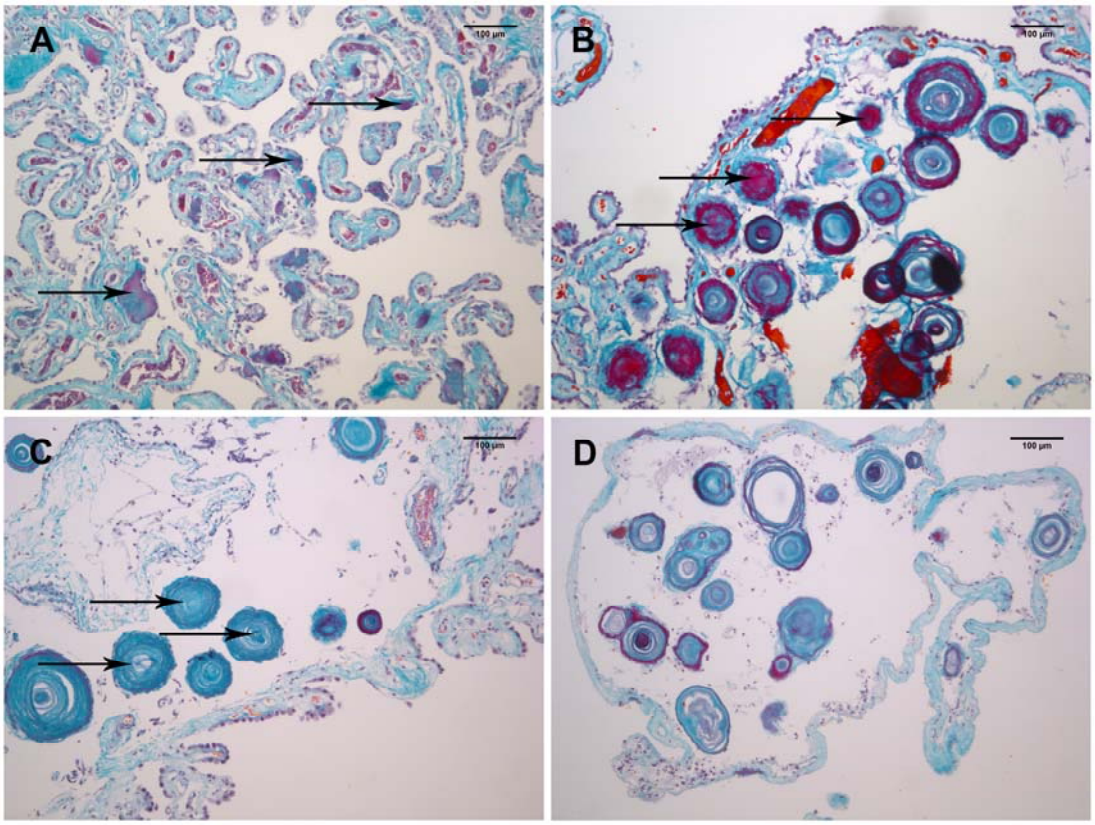

Fig. 1 – Psammoma bodies in choroid plexus (Mallory trichrome stain, × 10): A) amorphous calcifications; B) immature psammoma bodies; C) mature laminated psammoma bodies; D) cyst with psammoma bodies.

ventricle's choroid plexus (aged 35, 44, 59 and 69) and one sample of the third ventricle's choroid plexus (aged 44). These samples were excluded from the morphometric study of PBs.

Morphometric analysis

In order to analyze the ageing characteristics of choroid plexus, cases were divided into three age groups: Group I (35–50 years), Group II (51–70 years) and Group III (71–84 years). Due to the significant deviation from normal distribution, morphometric data are shown as median and interquartile range.

Left and right lateral cerebral ventricles' choroid plexus morphometric analysis

The results of the lateral ventricles' choroid plexus morphometric study are presented in Table 1. PBs diameter ranged from 145 μm to 357 μm. As it can be seen, there were some significant differences between left and right-side choroid plexus, but only in the young and middle-aged. Right lateral ventricle's choroid plexus was characterized with larger numeric density of in the first age group ($p < 0.001$), while in the second one the PBs became larger (area, perimeter and Feret's diameter) ($p < 0.001$) compared to the left side. In the oldest age group, such differences were not observed. With age, right choroid plexus surface density decreased ($p < 0.05$), while the PB volume density increased ($p < 0.05$).

Third and fourth cerebral ventricles' choroid plexus morphometric analysis

The results of the third and fourth ventricles' choroid plexus analysis are presented in Tables 2 and 3, respectively. The size range of the PBs in V3 was similar to the LV (149–340 μm), while in the V4 the PBs as small as 99 μm in diameter were found. A decrease in the blood vessels volume density was observed in the third ventricle's choroid plexus ($p < 0.05$), as well as an age-related decrease in PB perimeter ($p < 0.01$). There were no statistically significant changes during ageing in the choroid plexus of the forth ventricle during age.

The association of age, sex and psammoma bodies morphometric parameters with changes in the choroid plexus

There was no difference in the distribution of sexes among age groups ($\chi^2 = 5.640$, $p = 0.060$). We performed univariate linear regression in order to determine the relevance of age, sexand PBs morphometric parameters (APB, PPB, FDPB, NVPB and VDPB), as independent variables, in predicting the changes in the choroid plexus. For each of the independent variables (SDCP, VDBV), a separate model was created (Table 4).

A total of 50.9% of SDCP variance could be explained with these independent factors ($F = 13.213$, $p < 0.001$). The following variables were shown to independently predict SDCP: sex and three of the PBs dimensions (APB, PPB,

Table 1

Morphometric analysis of lateral ventricles' choroid plexus and psammoma bodies (PBs) across three age groups

Morphometric parameters	Left lateral ventricle's choroid plexus [Right lateral ventricle's choroid plexus]			
	Group I (35–50 years)	Group II (51–70 years)	Group III (71–84 years)	χ^2 (*p*)
SDCP (1/mm)	12.40 (8.08–14.92) [11.17 (8.85–16.29)]	14.08 (8.83–15.46) [12.89 (10.99–18.48)]	9.38 (6.46–11.86) [8.48 (7.36–9.99)]	2.143 (0.343) 6.964 (0.031)
Left vs. Right (*p*)	0.897	0.738	0.897	
VDBV (mm^3)	13.29 (9.32–16.25) [13.43 (9.92–19.90)]	12.92 (8.31–15.47) [11.32 (8.88–16.68)]	9.40 (7.19–10.40) [8.56 (7.65–12.05)]	2.143 (0.343) 3.750 (0.153)
Left vs. Right (*p*)	0.738	0.897	0.738	
APB (mm^2)	47.71 (29.37–60.60) [40.84 (29.70–50.14)]	41.16 (27.13–69.60) [58.71 (38.25–64.45)]	39.50 (37.96–49.22) [51.37 (44.55–61.79)]	0.536 (0.765) 3.750 (0.153)
Left vs. Right (*p*)	0.897	0.000	0.500	
PPB (mm)	0.75 (0.58–0.84) [0.54 (0.60–0.77)]	0.70 (0.54–0.89) [0.82 (0.67–0.86)]	0.71 (0.67–0.77) [0.77 (0.72–0.87)]	0.536 (0.765) 3.750 (0.153)
Left vs. Right (*p*)	0.897	0.000	0.738	
FDPB (mm)	0.25 (0.20–0.29) [0.23 (0.20–0.26)]	0.24 (0.19–0.30) [0.28 (0.23–0.29)]	0.24 (0.23–0.26) [0.26 (0.25–0.30)]	0.536 (0.765) 3.750 (0.153)
Left vs. Right (*p*)	0.897	0.000	0.738	
NDPB ($1/mm^3$)	13.43 (9.95–20.10) [14.32 (10.03–32.77)]	27.15 (9.42–36.46) [9.23 (7.61–18.41)]	19.95 (15.98–25.80) [19.07 (14.44–26.39)]	2.143 (0.343) 3.750 (0.153)
Left vs. Right (*p*)	0.000	0.738	0.500	
VDPB (mm^3)	4.10 (2.21–5.05) [4.10 (2.81–6.14)]	6.26 (2.79–8.53) [3.82 (1.42–6.48)]	6.62 (4.30–7.90) [6.45 (6.27–7.46)]	2.143 (0.343) 8.571 (0.014)
Left vs. Right (*p*)	0.738	0.500	1.000	

Results are given as median (interquartile range)

SDCP – surface density of choroid plexus; VDBV – volume density of blood vessels; APB – average area of PBs; PPB – average perimeter of PBs; FDPB – average Feret's diameter of PBs; NDPB – numeric density of PBs; VDPB – volume density of PBs.

Table 2

Morphometric analysis of the third ventricle's choroid plexus and psammoma bodies (PBs) across three age groups

Morphometric parameters	Group I (35–50 years)	Group II (51–70 years)	Group III (71–84 years)	χ^2 (p)
SDCP (1/mm)	16.81 (10.83–19.63)	19.25 (14.92–22.37)	13.53 (10.31–17.33)	0.400 (0.819)
VDBV (mm^3)	11.23 (10.63–14.69)	8.64 (7.79–11.84)	8.45 (8.36–11.09)	6.000 (0.050)
APB (mm^2)	35.16 (26.31–49.37)	34.32 (16.37–61.05)	24.12 (21.57–27.11)	3.000 (0.223)
PPB (mm)	0.64 (0.58–0.73)	0.61 (0.44–0.83)	0.54 (0.50–0.55)	9.200 (0.010)
FDPB (mm)	0.22 (0.20–0.25)	0.22 (0.15–0.29)	0.19 (0.18–0.20)	3.000 (0.223)
NDPB ($1/mm^3$)	9.87 (9.21–10.41)	6.58 (0.92–12.58)	20.60 (7.56–28.53)	3.600 (0.165)
VDPB (mm^3)	1.97 (1.55–2.47)	0.52 (0.19–1.67)	2.86 (0.82–3.69)	3.000 (0.223)

Results are given as median (interquartile range)

SDCP – surface density of choroid plexus; VDBV – volume density of blood vessels; APB – average area of PBs; PPB – average perimeter of PBs; FDPB – average Feret's diameter of PBs; NDPB – numeric density of PBs; VDPB – volume density of PBs.

Table 3

Morphometric analysis of the fourth ventricle's choroid plexus and psammoma bodies (PBs) across three age groups

Morphometric parameters	Group I (35–50 years)	Group II (51–70 years)	Group III (71–84 years)	χ^2 (p)
SDCP (1/mm)	19.45 (15.91–19.45)	19.37 (14.98–19.37)	17.82 (12.76–19.60)	2.396 (0.302)
VDVB	10.21 (8.64–10.21)	8.68 (7.75–8.68)	7.21 (6.30–12.12)	0.782 (0.676)
APB (mm^2)	19.40 (10.68–19.40)	28.54 (11.39–28.54)	42.10 (8.18–49.58)	0.782 (0.676)
PPB (mm)	0.43 (0.38–0.43)	0.60 (0.38–0.60)	0.71 (0.32–0.79)	0.782 (0.676)
FDPB (mm)	0.16 (0.14–0.16)	0.21 (0.14–0.21)	0.24 (0.11–0.29)	0.782 (0.676)
NDPB ($1/mm^3$)	8.15 (0.81–8.15)	3.48 (2.30–348)	2.43 (0.58–5.72)	2.396 (0.302)
VDPB	2.10 (0.07–2.10)	0.74 (0.12–0.74)	0.18 (0.00–0.29)	2.396 (0.302)

Results are given as median (interquartile range)

SDCP – surface density of choroid plexus; VDBV – volume density of blood vessels; APB – average area of PBs; PPB – average perimeter of PBs; FDPB – average Feret's diameter of PBs; NDPB – numeric density of PBs; VDPB – volume density of PBs.

Table 4

Univariate linear regression of choroid plexus parameters in function of age, sex, location and psammoma bodies (PBs) characteristics

Parameters		Unstandardized coefficients		Standardized coefficients			Model		
		B	SE	Beta	*t*	*p*	F	*p*	Adjusted r^2
SDCP (1/mm)	Constant	18.853	2.230		8.454	0.000	13.213	0.000	0.509
	Sex (male)	2.720	1.024	0.283	2.656	0.010			
	Age	-0.044	0.034	-0.138	-1.298	0.200			
	APB	0.143	0.066	0.632	2.175	0.034			
	PPB	-12.256	5.754	-0.627	-2.130	0.038			
	VDPB	-1.110	0.189	-0.628	-5.858	0.000			
VDVB	Constant	16.371	1.902		8.607	0.000	6.758	0.001	0.226
	Age	-0.097	0.028	-0.043	-3.393	0.001			
	PPB	47.587	21.584	3.276	2.205	0.032			
	FDPB	-134.779	63.448	-3.166	-2.124	0.038			

SDCP – surface density of choroid plexus; VDBV – volume density of blood vessels; APB – average area of PBs; PPB – average perimeter of PBs; FDPB – average Feret's diameter of PBs; VDPB – volume density of PBs.

VDPB). We found SDCP to be lower in males ($p < 0.01$). Surprisingly, the increase in APB predictedan increase in SDCP ($p < 0.05$), opposite to the PPB and VDPB which were inversely correlated to SDCP ($p < 0.05$ and $p < 0.001$, respectively).

In the case of the VDBV as the dependent variable, 22.6% of its variance was explained by the model (F = 6.758, $p < 0.001$) including age and the PBs' perimeter and Feret's diameter. All of these variables were shown to be statistically significant as independent predictors. Higher PPB was associated with higher VDBV ($p < 0.05$). One the other hand, with age and the increase in Feret's diameter of the PBs, there was a decrease in blood vessels volume density ($p < 0.001$ and $p < 0.05$, respectively).

Discussion

Psammoma bodies have never been observed in prenatal tissue samples, nevertheless, by the end of the 1st year, small ones start to concentrate around the vascular stock. Logically, in older specimens, larger ones are located centrally, often in cystical formations. On the other hand, peripherally, in choroidal villi beneath the CP epithelium, the PBs are significantly smaller [24]. The incidence of PBs findings on computed tomography (CT) scans rises from 0.5% to 86% from the 1st to the 8th decade [25]. Psammoma bodies consist of collagen whorls, 50–150 μm in diameter, but often even larger than 300 μm. Lamellar structure is the result of irregularcalcium deposition and reflects the time needed for a PB to be formed. Therefore, the mineral component is mostly calcium (phosphate and hydroxyapatite), but iron, magnesium, zinc and manganese are also present [26, 27]. Studies on the organic ingredients prove the incorporation of light-chain amyloid [17], associated with Alzheimer's disease. The maturity of the PBs may be evaluated by the presence/absence of the amorphous core. It is suggested that the immature PBs arise from the amorphous calcifications. Further deposition of connective fibers leads to the lamification and maturation of the PBs. Non-related to the age, larger and more mature PBs are associated with more intense changes on the CP epithelium.The presence of large PBs is realted to more prominent changes in the CP epithelium: extreme flattening, presence of cysts, larger vacuoles often deforming the cell and dislocating the nucleus [22, 28].

The presence of numerous PBs and the PBs with higher average area is not age-related [28]. In our study, we have found that the PBs volume density increases with age in elderly humans (beyond 70 years) in the right LV. Besides, there was a progressive decrease in the PBs perimeter during ageing in the V3. In accordance with the morphometric findings on the PBs, there was a decrease in surface density of the CP in the right LV which may be explained by the destruction of choroidal villi following the increased PBs formation. A decrease in blood vessels volume density in the V3 was noted as well, due to the thickening of the vessels walls [8] and, therefore, diminishing their caliber. Interestingly, there were significant differences between left and right lateral ventricles' CP, in terms of the PBs size and numeric density, which was also reported in the literature [25]. If we take into account the hypothesis of the circulating agents inducting connective tissue activation [22], differences in the blood flow may result in the various speed and intensity of the PBs formation. These differences were noted in the first two age groups, suggesting that it is relevant only in the view of age at which new PBs start to form and mature. As the whole process progresses, these differences disappear.

Our findings suggest that the CP degeneration due to the shortening of the choroidal villi [4] is not age-related, but is well correlated with the PBs formation. Other factors, such as sex, contribute to the prediction of the CP size. We have found surface density of the CP to be smaller in male specimens. The impact of sex hormones on the CP and cerebrospinal fluid is well documented, describing the sex differences in circadian rhythm signalling, the CP barrier function, its metabolism and stem cell differentiation [29]. Volume density and perimeter of the PBs are found to be strongly correlated

with a decrease in the SDCP. Bigger PBs (their perimeter) and more densely packed, seem to be a good predictor of the CP impairment. On the other hand, the decrease in the density of blood vessels seems to be a direct consequence of ageing. Age-related changes in the CP (probably the thickening of the basal membrane and the surrounding increased stromal reaction [8, 22]), in combination with the PBs of the large FDPB, may cause the diminishing of blood supply into the CP.

Conclusion

As a summary, we want to point out there is an association between ageing and increased size and volume density of psammoma bodies. More important is the fact that the PBs presence and their morphometric characteristics are good predictors of changes occurring on the level of choroid plexus structure and vascularization, which may have crucial effects on the CP physiology.

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