

Cavum Septi Pellucidi as a Marker of the Neuropsychiatric Diseases: A Pointer or Misdemeanor? A Cadaveric – Clinical Observation

Branislav Filipovic^{1,2*}, Nikola Ilankovic^{1,3}, Ana Starcevic^{1,2}, Branka Filipovic^{1,4}, Lazar Stijak^{1,2}, Laslo Puskas^{1,2} and Tatjana Atanasijevic^{1,5}

¹University of Belgrade, Faculty of Medicine, Belgrade, Serbia

²Institute of Anatomy "Niko Miljanic", Belgrade, Serbia

³Institute of Psychiatry, Clinical Center of Serbia, Belgrade, Serbia

⁴Clinical and Hospital Center Bezanijska Kosa, Belgrade, Serbia

⁵Institute for Forensic Medicine, Belgrade, Serbia

Abstract

Cavum Septi pellucid (CSP), a cavity between the laminae of the septum pellucidum, for a longer period has been reported as an anomaly of the brain midline, associated with neuropsychiatric diseases, mostly schizophrenia, but also posttraumatic stress disorder, De la Tourette disease, and persons who survived a repeated a serious head trauma, boxers on the first place. Our investigation has been performed on 479 unfixed frozen brains, of the autopsied individuals of both genders, and MRI scans of 250 examinees, out of which 110 had neuropsychiatric illness. In our sample, the prevalence of CSP was 22.96% among the autopsied individuals and 9.2% in examinees who underwent MRI scan. The cause of the death among schizophrenia suffering persons was suicide (18 out of 25 patients). Obviously, CSP is more frequently associated with neuropsychiatric diseases, but a dilemma still exists, did we make a bias in brain suitability for the examination or we did the same mistake in observing clinical cases. A large CSP, though, is an almost certain sign for an underlying neuropsychiatric impairment, especially schizophrenia. The CSP among alcoholics and persons with the prior sustained head blows is probably of the same cause and represents an aftermath of the diffuse axonal injuries, i.e. brain trauma.

Keywords: Septum pellucidum; Cavum; Autopsy; MRI; Suicide

Introduction

Cavum Septi pellucid (CSP), a cavity between the laminae of the septum pellucidum, for a longer period has been reported as an anomaly of the brain midline, associated with neuropsychiatric diseases, mostly schizophrenia, but also posttraumatic stress disorder, De la Tourette disease [1], and persons who survived a repeated and serious head traumas, boxers or aggressive individuals [2,3]. The septum pellucidum, a component of the limbic system, is a thin plate of two laminae that forms the medial walls of the lateral ventricles. When these laminae fail to fuse, they form a cavity known as cavum septum pellucidum (CSP) [4]. Cavum septum pellucidum is present in 100% of fetuses and premature infants, but the posterior half of the leaves are normally fused by the age 3-6 months [5]. The presence of a CSP later in life might reflect developmental abnormalities of structures bordering the septum pellucidum, such as the corpus callosum and hippocampus [6]. Thus, the CSP can be considered a marker of limbic system dysgenesis, either a form of midline abnormalities, or both [7]. The complete fusion defect of the two leaflets of the septum pellucidum—an anomaly termed combined CSP and cavum vergae (CV)—is considered the most extreme form of CSP, mostly known as cyst of septum pellucidum.

Contradictory results were also evident when considering the prevalence of large CSPs: rates vary from 0 [8] to 11.5% [9] in healthy individuals, and from 4.1% [10] to 36.4% [11] in patients with the disease from schizophrenia spectrum. Increased prevalence of enlarged cava septi pellucidi were obtained in affective and schizotypal disorder, Tourette syndrome, posttraumatic stress disorder and other neuropsychiatric impairments [1,11,12]. Other results are more or less based on the isolated cases and could not be considered for a serious study of the prevalence.

Previously published results on the autopsy material showed that individuals with schizophrenia and large cava septi pellucidi more frequently commit suicides [13].

Our aim was to compare results obtained from the autopsy material and MRI scans of the patients in order to show potential differences between the samples and to discuss the reasons for their existence.

Methods

Subjects

The autopsy group: The investigation was performed on 479 autopsied cadavers (310 male and 169 female), aged 22 to 89 (mean 57.44 ± 15.37). The main criterion for the selection of brain suitability for this study was the absence of macroscopic changes on brain parenchyma and that time of death did not exceed 12 hours. Data obtained from families of the deceased, clinical and medical reports about neuropsychiatric diseases and disorders were matched with the intra-autopsy finding. The criteria for the diagnose settlement were used according to the Tenth Revision of International Classification of Diseases (ICD-10). In our sample 110 CSP were obtained, involving 40 normal individuals, 25 schizophrenia suffering patients, 25 alcoholics and 20 persons with verified prior head trauma (excluding the same diagnose as the cause of death). The subgroup of 58 cava longer or equal 6 mm, according to criteria proposed by Nopuolos and her team (1997), was abstracted and additionally analyzed. Sixteen (10 males and 6 females) belonged

***Corresponding author:** Branislav Filipovic, Institute of Anatomy "Niko Miljanic", 4/2 Dr. Subotica Starijeg, 11000 Belgrade, Serbia, Tel: +381112684259; E-mail: filipovic.branislav@gmail.com

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to the group without neuropsychiatric symptoms “*asymptomatic CSP*”, and 42 had at least one of neuropsychiatric disorders (“*symptomatic CSP*”), out of which eighteen (14 men and four women) suffered from schizophrenia, sixteen (11 men and 5 women) were alcoholics and eight (six males and two females) sustained at least one serious prior head trauma and subsequently manifested posttraumatic aggressive behavior. Demographic data are shown in the Table 1.

All the families of deceased signed a written consent about being familiar with the goals of the study and the agreement that data about their family member could be used in this investigation.

Individuals who underwent MRI scan: The other group has been formed of 250 individuals, 130 males and 120 females, and contained 110 psychiatric patients and 140 healthy controls, normal by current standard. Patients were treated in the Institute of Psychiatry, Clinical Center of Serbia and in Private psychiatric clinic “Katarza”, from February 2003 to December 2010 (Table 2).

Quantitative methods: Unfixed frozen brains were cut axially on Leica CM3600 Whole Body Sectioning Cryo Macrotome, to 1.5 mm thick slices. When present, CSP on such sections were mostly triangular in a shape. Measurements on priory digitalized picture of the slices were taken on every slice with CSP, and a mean value was marked

as a definitive in the data base. All the measurements were provided by Scion Image, Scion Inc, USA, a freeware, version 4.0.3.2 with the adjustment of measures with the scale mark on each photography. Clefts at least 2 mm (mean value) long and wide were considered as *cavum septi pellucidi* and were included in this study.

Whole brain MRI scans were obtained with a 1.5 Tesla Siemens Somatom magnet using a three-dimensional spoiled gradient recall acquisition (SPGR; TE=13 msec, TR=38 msec, flip angle=45°, number of excitations=1), which yielded a series of 124 contiguous, 1.5-mm coronal slices with an in-plane field of view of 24 cm and a 256×256 matrix.

CSP ratings: Two raters, blind to group membership, determined the presence (on at least one 1 mm coronal slice), length (total number of contiguous slices on which it was present) [14], and grade of the CSP [1,11].

Statistical data processing has been done by SPSS statistical software (SPSS Inc, Chicago, IL).

Results

Prevalence

Total prevalence in the autopsied population was 22.96% (110 out

Characteristic	With CSP (Prevalence)	Male (Prevalence)	Female (Prevalence)	Without CSP (%)	Male (%)	Female (%)
Sample (N=479, 310 males, 169 females)	110 (22.96)	75(24.19)	35 (20.71)	369 (77.04)	235 (75.81)	134 (79.39)
Large CSP (% out of total CSP)	58/110 (52.73)	41/75 (54.66)	17/35 (48.57)	-	-	-
Age total 57.44 ± 15.37	54.13 ± 14.55	53.27 ± 10.15	55.61 ± 9.14	59.67 ± 14.88	58.57 ± 8.56	61.26 ± 10.23
Age	52.25 ± 13.24	51.04 ± 11.17	54.21 ± 12.22			
Asymptomatic (normal by standard)	16/60 (26.67)	10/42 (23.81)	6/18 (33.33)	337/369 (91.32)	211/235 (89.79)	126/134 (94.03)
Symptomatic cava ≥ 6.0 mm						
Schizophrenia*	18/44 (40.91)	14/32 (43.75)	4/12 (33.33)	5/32 (15.62)	4/24 (16.67)	1/8 (12.5)
Alcoholism**	16/44 (36.36)	11/32 (34.38)	5/12 (41.67)	12/32 (37.50)	9/24 (30.75)	3/8 (37.5)
Brains with past head trauma**	10/44 (22.73)	7/32 (21.87)	3/12 (25)	15/32 (46.88)	11/24 (45.83)	4/8 (50)
Symptomatic cava	44/60 (73.33)	32/42 (76.19)	12/18 (66.67)	32/369 (8.67)	24/235 (10.21)	8/134 (5.97)
TOTAL	60/110 (54.54)	42/75 (56)	18/32 (51.43)	369	235	134

Relative risk=15.78, **RR=23.24, ***RR=9.39, OR 4.52-19.38.

Table 1: Demographic data for the autopsy sample obtained in the study.

Characteristic	With CSP Total (prevalence)	Male (prevalence)	Female (prevalence)	Without CSP Total	Male	Female
Sample (N=250, 130 males, 120 females)	23/250 (9.2)	18/130 (13.85)	5/120 (4.17)	217/250 (86.8)	112/130 (86.15)	115/120 (95.83)
Large CSP	10/23 (43.48)	10	0			
Age total 55.44 ± 13.39	49.13 ± 12.15			57.67 ± 16.39		
Age	52.25 ± 13.24					
Asymptomatic cava (normal by standard)	0 (0/0)			217 (112/115)		
	Symptomatic cava ≥ 6.0 mm			Without CSP		
Schizophrenia	4 (40)	4	0	42 (34/8)		
Alcoholism	1 (10)	1	0	20	11	9
Brains with past head trauma	2 (20)	2	0	0		
PTSD						
De la Tourette sy	1 (10)	1	0	17	9	8
Bipolar disorder				0		
	1 (10)	1	0			
	1 (10)	1	0	8 (1/7)	1	7
Total	10 (10/0)			87 (55/32)		

Table 2: Demographic characteristics of the population analyzed by MRI.

	MRI			Autopsy		
	No (%)	Male*	Female	No (%)	Male (%)	Female (%)
Asymptomatic	6 (46.15)	3	3	26/50 (52)	17/32 (53.13)	9/18 (50)
Schizophrenia	2 (15.38)	1	1	5/50 (10)	4/32 (12.5)	1/18 (5.56)
Alcoholism	1(7.69)	1	0	13/50 (26)	8/32 (25)	5/18 (27.78)
Brains with past head trauma	2 (15.38)	1	1	6/50 (12)	3/32 (9.38)	3/18 (16.67)
Bipolar disorder	2 (15.38)	1	1	/		
Total	13	7	6	50	32	18

*Number of examinees was too small for accurate percentage calculation

Table 3: Small (<6 mm) cava septi pellucidi in the groups obtained.

of 479 brains), among which 60 cava were larger than 6 mm. Overall prevalence among MRI scanned population was 9.2% (23 out of 250 brains). The difference in appearance was statistically highly significant. Chi square=20.865, degrees of freedom=1, p=0.000.

Large CSPs in the autopsied population appeared in 60 cases, while the same structure was noted in 10 cases among patients who underwent MRI scans, although this time chi square failed to confirm the difference: Chi square=0.9346, df=1, p=0.333 (Tables 1 and 2). Distributions of the CSP smaller than 6 mm are presented in the Table 3.

Relative risks

Relative risks were computed only for the population examined during autopsies and for large cava septi pellucidi.

For schizophrenia patients, relative risk was 15.78, Odds Ratio (OR) 9.66 to 25.78, for the examinees who suffered from alcoholism RR=23.24; OR 12.8-42.29 and for the persons who survived at least one serious head blow RR=9.39, OR 4.52-19.38.

Causes of death

In the entire population with CSP, 18 individuals committed the suicide, 10 suffered from schizophrenia and in 7 of them (5 males and 2 females) large CSP was noted. Number of homicide victims among persons with CSP was 18, and mention death cause was dominant among persons who survived at least one serious head blow (Table 4). 58 persons with CSP died accidentally, most of them belonged to the group normal by current standards (c/s), while 16 of them died of the death of the natural cause, mostly persons addicted to alcohol. Among controls without CSP, accident was the dominant form of the death (257 cases) and the rate of suicide and homicide was almost equal (44 and 43 cases, respectively).

Chi square revealed uneven distribution of the death causes among persons with CSPs: chi square=55.69, df=9, p=0.000.

Discussion

The purpose of the paper is the comparison of prevalence of the appearance of CSPs in autopsied individuals and patients treated from neuropsychiatric diseases, who underwent MRI scanning.

Several studies [11,14-16] but not all [8-10,17,18] studies using high-resolution MRI have reported an increased prevalence of a large CSP in schizophrenia. The reason for these discrepancies, obtained even in our results, is unclear because most studies used basically the same definition for a large CSP (≥ 6 mm), and we can only speculate that the pitfall lays in the way and criteria in patient selection for the study, thus certain authors claimed that selection bias even determines the CSP prevalence, moreover the postmortem studies as stressed as seriously biased *per se* [19]. On the other side, some guidelines for clinical examination might be a limitation factor: the patients with

conspicuous clinical symptomatology of the psychiatric illness mostly do not undergo MRI scanning, furthermore not too many persons with the neuropsychiatric disturbance undergo autopsy, except if they were victims of the violent death, suicide or accident, for example. This fact partially explains the figures related to the suicide rate among patients with schizophrenia and the relatively high number of CSPs in the current study. In our country, the guidelines of the good practice for the diagnostic procedure for newly obtained patients with schizophrenia do not involve the mandatory MRI scanning prior to the therapy proscriptio, and, in our opinion, this procedure should be included for each schizophrenia suffering individual. On the other side, the obligation for the autopsy of each psychiatric patient who died in hospital should be introduced.

Posttraumatic CSPs could also be a sign of the diffuse axonal lesions. The largest frequency of CSP found in fatal victims of head trauma, particularly in patients with severe diffuse axonal lesion (grades 2 and 3), when compared with the individuals without a history of head trauma, suggests that the high-intensity angular acceleration of the head causes complementary and independent displacement of the cerebral hemispheres and dislocation of one of the leaves of the septum pellucidum on the other. This could result in separation of the two leaves and formation of CSP, usually cleft in shape [20]. The same pathophysiological mechanism might be involved in genesis and consecutive higher prevalence of CSPs, related to the boxing population [3,21]. The possibility of the neurodevelopmental axonal lesions in patients with schizophrenia and possibility of the diffuse axonal lesions in patients with alcoholism, as a result of their behavior (fights, accidents), or metabolic consequence of alcohol intake, as Wernicke's encephalopathy is also the subject for further discussion, but, so far, is only at the level of speculation. Both diseases are involved with the revealed volume reduction of fornix [22], and corpus callosum [23], structures the septum pellucidum is spread in between.

Presence of the CSP and absence of interthalamic adhesion recently became attractive for the investigations, either in schizophrenia suffering persons, or in patients with bipolar, major depressive mood and borderline personality disorders [15,24-26]. As previous investigators did not report this combination related to the alcoholism and survived head blows, we did not take into the consideration absence of the adhesion interthalamica for this study.

It has been assessed that patients with schizophrenia and related disorders have been found to be at higher risk of both being physically violent to others and becoming a victim of physical violence themselves [27-30]. Our question is: "Could mentioned violent treatment cause brain trauma similar to those obtained in boxers or ones mentioned by Pitella and Gusmão [20]"

In conclusion, large cavum septi pellucid, when obtained during an autopsy procedure, is the putative marker of neuropsychiatric diseases, on the first place schizophrenia. Also, generally, it is a pointer

of the disturbed brain due to the alcoholic changes or the aftermaths of the survived head blows. Its appearance is possibly related to the diffuse axonal destruction of the various etiologies that affected two anatomical structures supporting the septum pellucidum: fornix and corpus callosum. One dilemma still remains: does the CSP point towards one of the mentioned neuropsychiatric diseases, or just to the survived brain trauma, because the lower rate of CSP revealed on MRI scans maybe supports the latter statement.

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