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Original Article

Morphological and clinical features of small cava septi pellucidi: a post mortem study

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ABSTRACT

Small cava septi pellucidi (CSP) are sometimes automatically regarded as an anatomical variation (asymptomatic CSP), especially if they could not be associated with a neuropsychiatric disorder, like schizophrenia or alcoholism (symptomatic CSP). Our aim was to investigate the impact of symptomatic CSP in the population in which CSP length was less or equal to 6 mm (criterion established by Nopoulos et al in 1997).

We have overlooked 479 post mortem brains that underwent serial frozen sections in the axial plane on 1.5 mm of thickness. A sample of 110 CSP was obtained, among which 50 were adequate for this study.

In our sample, 26 CSP were asymptomatic, 13 were on alcoholic brains, 6 were obtained from subjects who faced one or several head trauma and later manifested aggressive behavior, and remaining 5 belonged to schizophrenics. There were no major differences in lengths and widths measured, except between the lengths of CSP in schizophrenics and alcoholics ($p<0.05$, Bonferroni post hoc correction).

Cava shorter or equal to 6 mm were normal variation in more than a half of our sample. Symptomatic CSP had a representative impact of 48%, out of which majority was revealed in alcoholics. We suggest a precaution before classify a small CSP into anatomical variations. ***Neuroanatomy; 2006; 5: 8–11.***

Key words [septum pellucidum] [cavum] [schizophrenia] [alcoholism] [head trauma]

Introduction

The *septum pellucidum* (Eng. "the pale membrane"), thin, two-leaflet translucent membrane on the medial wall of the frontal horn of the lateral ventricle, is believed to be a component of the limbic system. Its role is described as an important relay between limbic structures (hippocampus, amygdaloid complex), hypothalamic autonomic system and brain stem reticular formation [1–3]. The cavity between laminae, known as *cavum septi pellucidi* (CSP), is notable in almost 100% of examined fetuses, but in over than 85% it fuses by the age of three to six months [4–6]. When present in late childhood, adolescence or adult age, it represents a midline fusion defect of rather uncertain clinical significance. It was suggested that CSP, large ones in particular, should be considered a developmental anomaly, contributing to neurological and psychiatric disorders [3, 7, 8]. Increased prevalence of CSP was reported in schizophrenic patients [8–13], alcoholics [14] or brain injured people, particularly boxers [15–19].

Commonly, only larger CSP (>6 mm in length) were stressed as a putative marker of disturbed brain development and could be associated with a variety of neuropsychiatric illnesses [20, 21].

In this paper we have hypothesized that small CSP could also be related to certain neuropsychiatric disorders and that they could not be classified as "normal" in advance.

Material and Methods

The investigation was performed on 479 cadavers (310 male and 169 female), aged 22 to 89 (mean 57.44±15.37), autopsied in the Institute for Forensic Medicine at School of Medicine, University of Belgrade. The main criteria for the selection of brain suitability for this study were *a)* the absence of macroscopic changes on brain parenchyma and *b)* that time of death not exceeding 12 hours before autopsy. Data relating medical history were matched with the cause of death, determined after autopsy. Attention was paid to neuropsychiatric diseases and disorders, such as schizophrenia, alcoholism as well as to prior head traumas. The criteria for the settlement of the diagnosis were used according to the *Tenth Revision of International Classification of Diseases* (ICD-10). In our sample 110 cava septi pellucidi were obtained, from 40 normal individuals, 25 schizophrenics, 25 alcoholics and 20 people with a history of head injury associated with aggressive behavior. These diagnoses were not designated as (direct) cause of death. The subgroup of 50 cava shorter than 6 mm, according to criteria proposed by Nopuolos and her team [8], was abstracted and additionally analyzed. Twenty six people (17 males and 9 females) belonged to the group without neuropsychiatric symptoms *"asymptomatic CSP"*, and 24 had at least one of neuropsychiatric disorders (*"symptomatic CSP"*), out of which five (4 men and one woman) were schizophrenics, thirteen (8 men and 5 women) were alcoholics and 6 (three males and three females) sustained at least one

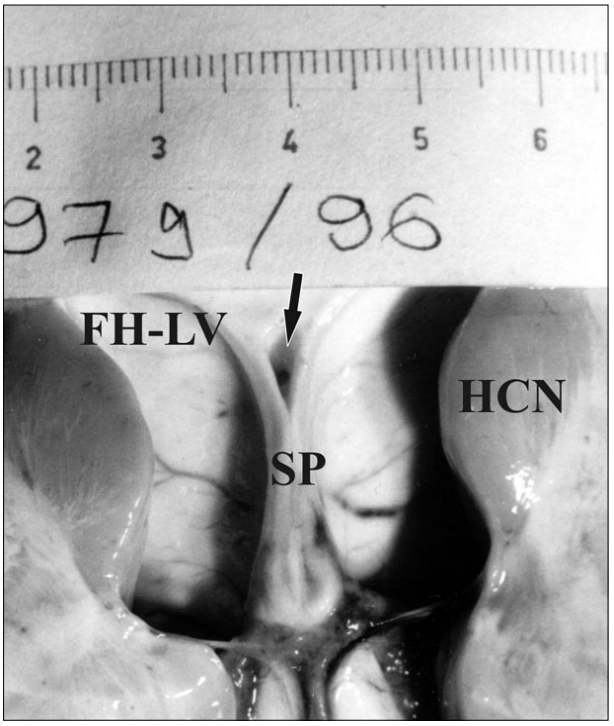

Figure 1. Horizontal section through small cavum septi pellucidi (arrow) of an alcoholic (male, 43) (***FH-LV:*** *frontal horn of the lateral ventricle;* ***SP:*** *septum pellucidum;* ***HCN:*** *head of the caudate nucleus).*

serious prior head trauma and subsequently manifested posttraumatic aggressive behavior.

Unfixed frozen (on –15°C) brains were cut axially, to one and a half millimeter thick slices. When present, CSPs on such sections were mostly triangular in shape. Measures were taken of every slice with CSP, and a mean value was marked as a definitive in the data base. *Length* (the approximate height of the triangle) and *width* (length of the base of the triangle) of CSP were obtained. Only clefts long at least 2 mm (mean value), were considered as cavum septi pellucidi, and were included in the study. During this study none of other midline brain malformations was found.

The differences of means obtained were tested by one-way analysis of variance (ANOVA) with post hoc Bonferroni correction for parametric, Student's t test, and chi-square and Fisher's exact probability test, for non-parametric data. The entire statistics was evaluated on 95% confidence interval.

Results

Prevalence

In our sample of 479 brains, 110 cava were obtained (total prevalence=22.96%) from 75 males and 35 females. Small cava were remarked in 50 cases (10.44% in the examined group, 45.45 % of the entire sample of CSPs), 32 males and 18 females. No statistically significant differences between genders were revealed in relation to the frequency of both symptomatic and asymptomatic small cava: chi square=0.045, DF=1, p>0.05, and to the distribution of etiologically various types of symptomatic CSP; chi square=0.131, DF=3, p>0.05.

Asymptomatic cava were detected in 52% of brains with small CSP, while remaining 48% belonged to cava associated with pathology studied (Fig. 1). The detailed distribution was shown on the Table 1.

When compared numbers of symptomatic and asymptomatic small CSP with frequency of cava larger than 6 mm, chi square disclosed highly significant difference. Contrary to the nearly equal distribution of small CSP types, a high predominance of symptomatic large cava was found.

Statistical analysis of CSP type of symptomatic and asymptomatic CSP were compared: chi square=8.496, DF=1, p = 0.00358; Fisher's exact probability p=0.001734. Clear statistical difference was found when compared

Table 1. Distribution of small CSP in relation to the CSP type.

	ASYMPTOMATIC	SYMPTOMATIC (24 CSP)			TOTAL
		SCH	ALCH	PTAB	
Number	26	5	13	6	50
%	52	10	26	12	100

(SCH: Schizophrenia; ALCH: Alcoholics; PTAB: Brain injured with post-traumatic aggressive behaviour)

Table 2. Comparison of the distribution of symptomatic and asymptomatic small and large cava.

CSP Type	CSP Size		
	Small	Large	TOTAL
Asymptomatic	26	14	40
Symptomatic	24	46	70
TOTAL	50	60	110

(F test: upper probability = 0.001734)

Table 3. Comparison of the observed frequencies when symptomatic small and large CSP have been redirected into groups based on the psychiatric illness.

	Small CSP	Large CSP	TOTAL
Asymptomatic	26	14	40
Schizophrenics	5	20	25
Alcoholics	13	12	25
PTAB	6	14	20
TOTAL	50	60	110

(P < 0.001, chi square)

Table 4. Mean lengths and widths (±SE) in asymptomatic and symptomatic CSP (in millimeters).

CSP Type	CSP Measures (mean ±SE)	
	Length	Width
Asymptomatic	3.9±0.22	2.57±0.11
Symptomatic	4.21±0.27	2.67±0.12
t-test (SD)	p>0.05	p>0.05

(SE: standart error; SD: significance of difference)

Table 5. Means (±SE) and ranges of lengths in asymptomatic CSP, schizophrenics, alcoholics and people with prior head trauma and/or aggressive behavior (in millimeters).

CSP Type	CSP Measures (mm)					
	Length			Width		
	Mean ± SE	Minimum	Maximum	Mean ± SE	Minimum	Maximum
Asymptomatic	3.97±0.22	2.00	5.90	2.55±0.11	1.20	3.90
Symptomatic	2.83±0.27*	2.10	3.65	2.44±0.13	2.00	2.75
Alcoholics	4.58±0.28	2.00	6.00	2.69±0.17	1.70	3.80
PTAB	4.36±0.77	2.00	6.00	2.94±0.24	2.00	3.30

(Bonferroni post hoc test for schizophrenics and alcoholics p<0.05)*

groups with various symptomatic cava as follows: chi square=15.055, DF=3, p=0.00177 (Tables 2 and 3).

Linear parameters

Symptomatic cava were slightly longer and wider than asymptomatic, though these differences were not statistically significant: *length:* 4.21 versus 3.9 mm mean values, t= –0.925, DF=48, p>0.05; *width:* 2.67 vs. 2.57 mm; t=0.603, DF=48, p>0.05, respectively (Table 4). ANOVA revealed statistically significant difference between lengths, when symptomatic CSP were divided in illness subgroups: F3, 46=3.028, p<0.05, respectively, whereas for widths values remained insignificantly different. Bonferroni post hoc test emphasized difference between lengths in schizophrenics and alcoholics (p<0.05), while there was no statistical significance for all other groups (p>0.05, Table 5).

We did not get any of gender differences in linear parameters. Mean length ± standard error (SE) in males was 4.06±0.23 mm and in females 4.04±0.28 mm (t=0.057; DF=48, p>0.05). Mean width in males was 2.56±0.098 and in females 2.72±0.16 mm (t= –1.004; DF=48, p>0.05).

Discussion

This study reveals that little bit less than a half of cava smaller than six millimeters in length is interfered with some neuropsychiatric pathology: schizophrenia, alcoholism or aggressive behaviour developed after brain trauma. Also, the probability of interconnection of aforementioned disorders with CSP appearance is higher when larger CSP are obtained. Criteria established by Nopoulos and her coauthors [8], afterward accepted by Kwon et al and Rajarethinam et al [20, 22], that CSP longer than 6 mm could in advanced be treated as *symptomatic* (we suggest this term instead *"abnormal"*) seemed also to be appropriate for this investigation. Statistical evaluation of the frequency demonstrated that a large CSP is more likely "symptomatic" than the small one. Nevertheless, symptomatic cava are taking a respectable part among small cava, as well. It appears that small cava are characteristic for brains in alcoholics. This, perhaps, could be attributed to intensive global demyelinization, particularly involving corpus callosum [23]. Process of demyelinization escalates in, often fatal, Marchiafava–Bignami disease, affecting corpus callosum, cortico-cortical and cortico-subcortical connections [24]. The developmental mutuality between corpus callosum (Eng. "the blistered body") and septum pellucidum [25] might be a trace for the explanation of CSP appearance in alcoholics. The higher prevalence of small CSP, moreover, could be explained by the fact that septum pellucidum is not deteriorated directly by the ethanol or malnutrition, but the subsequent separation of its laminas is the consequence of severe myeline loss in rostrum, and, particularly, genu of corpus callosum [23, 26]. Smaller CSP, appeared to be common in people with at least one serious head blow in lifetime, which was frequently combined with aloanamnestic confirmation for tendency to aggressive behavior. Three people from this group were verified as drug addicts, and for the rest of them such data could not be obtained. Many authors [15, 17, 19, 27], stated that CSP is a result of survived repeated head blows, particularly among boxers, and that it might be a sign of *"dementia pugilistica"* (derived from Latin word *pugilatus*, the fist fighting). We could only suggest the possible relationship between the severity (accompanied by conscience loss or not) and frequency of such head trauma and the length of CSP. Such association should be investigated, if the limitations of post mortem study could be overcome. We can assume that cava among alcoholics and individuals sustained head trauma could be also treated as *"acquired CSP"*.

Definitely, CSP in schizophrenics ought to be observed independently from those in alcoholics and head blow survivors and could be labeled as a developmental anomaly. Only one fourth of schizophrenia diagnosed people in our sample had a small CSP. The CSP in schizophrenics were shorter than those in alcoholics, but this difference could be accidental and a consequence of relatively small number of CSP in studied schizophrenics that were less than 6 mm in length. Our relating coincidental nature of this association is supported by the lack of significance in difference of widths. The similar observation was reported by Rajarethinam et al; they stated that the prevalence of "any CSP" was higher in schizophrenics, but the high prevalence of larger cava are possibly among decisive factors for the confirmation of the neurodevelopmental theory of schizophrenia [22]. In addition, an often seen comorbidity between alcoholism

and schizophrenia leads to serious compounded brain volume deficit of prefrontal and temporal cortices [28], although cava septi pellucidi in both groups have been obtained as significantly different [29, 30]. This finding urged our suggestion about the subcortical consequences of this compound effect and possibility that small CSP in schizophrenics be a reflection of accompanying alcoholism. It may represent a respectable challenge for future investigations.

In conclusion, despite the fact that more than a half of the examined CSP were asymptomatic, the relatively high percentage of symptomatic cava septi pellucidi among CSP long equally or less than 6 mm indicates that they could not be treated as normal anatomical variation. Alcoholics were the dominant groups in our sample of small symptomatic CSP. Careful anamnesis ought to be directed toward eventual drinking problems is suggested if a small CSP is longer than 4 mm.

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