Eur Arch Psychiatry Clin Neurosci (2004) 254 : 295–302 DOI 10.1007/s00406-004-0496-z

ORIGINAL PAPER

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The septum pellucidum and its variants

An MRI study

Received: 16 April 2003 / Accepted: 16 January 2004

Abstract *Purpose* Increased prevalence of cavum septi pellucidi (CSP) in schizophrenic patients in comparison to healthy subjects was reported previously. Our purpose was to evaluate the prevalence of variants of the septum pellucidum in healthy subjects in three different age groups. *Methods* 151 healthy subjects, including 46 children (age 6 ± 4 years), 72 young adults (age 31 ± 8 years) and 33 elderly adults (age 59 ± 7 years) were examined with high-resolution MRI. Three observers analysed the images using a standardised protocol. We evaluated the incidences of CSP, cavum vergae (CV) and their length. *Results* CSP was detected in 80 % of the cases in the paediatric group and 68 % of young adults and in 72 % of the elderly adults. A cavum vergae (CV) was noted in 22 % of the children, in 39 % of the young adults and in 36 % of the elderly subjects. There was no significant difference between the age-related groups. *Conclusion* We detected a high prevalence of cavum septi pellucidi without a significant age dependence. Enlarged cava septi pellucidi are rare in healthy subjects.

Key words cavum septi pellucidi · cavum vergae · septum pellucidum · cysts · MRI

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Introduction

Several previous studies reported an association of cerebral midline malformations and psychotic disorders. Specific developmental brain anomalies associated with, e. g. schizophrenia include corpus callosum dysgenesis [1, 2] and grey matter heterotopia [3]. Further studies reported an increased frequency of enlarged cava septi pellucidi (CSP) in patients with schizophrenia [1, 4–8]. However there is an enormous variability concerning the incidence of CSP in patients as well as healthy volunteers between these studies. Table 1 summarises the incidences of CSP in healthy subjects recently reported in postmortem and MRI studies. Most of these studies, however, included small groups of healthy controls. Studies reporting incidences in representative, large populations of healthy subjects based on high-resolution MRI are rare, especially considering the differentiation of various age groups. Filipovic et al. [9] investigated ageing changes of the cavum septi pellucidi in a postmortem study and reported no statistically significant differences between younger and elderly adults.

Table 1 Incidence of cavum septi pellucidi (CSP) in normal adults

Author	Year	Method	Sample	ST (mm)	Incidence
Van Wagenen	1934	Postmortem	N = 30		60 %
Schwidde et al.	1952	Postmortem	N = 1032		20 %
Hughes et al.	1955	Postmortem	N = 110		85 %
Shunk	1963	Postmortem	N = 307		60 %
Shaw and Alford	1969	Postmortem	N = 374		12 %
Degreef et al.	1992	Postmortem	N = 39		31 %
Degreef et al.[a]	1992	MRI	N = 46	3.1	2 %
Scott et al.[b]	1993	MRI/CT	N = 28/34	5.0	5.1 %
Jurjus et al.	1993	MRI	N = 37	5.0	19 %
DeLisi et al.	1993	MRI	N = 47	5.0	30 %
Nopoulos et al.	1997	MRI	N = 95	1.5	58.7 %

[a] only moderate to large CSP; [b] neurological patients

The aim of our study was to analyse the prevalence of cystic variants of SP in a representative population of healthy individuals with a range from infants to elderly individuals. We included three different age groups particularly with regard to a potential influence of brain development.

In order to elucidate this problem, embryology and anatomy of the septum pellucidum have to be considered [10, 11]:

The septum pellucidum (SP) is usually described as a thin vertical partition composed of two laminae. Seen from the side, the septum pellucidum has the shape of a triangle, its base located anteriorly and its apex posteriorly. It is attached cranially to the lower surface of the trunk of the corpus callosum, caudally and posteriorly to the anterior part of the fornix, caudally and anteriorly to the upper surface of the rostrum of the corpus callosum (Fig. 1a–c). Each lamina forms part of the medial wall of the anterior horn and central part of the respective lateral ventricle.

The development of the nervous systems starts with the neural tube, an ectodermal derivation. At the cranial end three vesiculae form the brain: First the rhombencephalon, second the mesencephalon and third the prosencephalon. The prosencephalon consists of the diencephalon and the telencephalon. The telencephalon includes the median lamina terminalis, which is the starting point for the commissures. The lamina terminalis is a thin plate in front of the primordium of optic chiasm, which can be seen at week four. One week later the commissural plate appears as a thickening in the embryonic lamina terminalis. The commissural plate, which is an integral part of the telencephalon medium, is the route by which fibres pass from one cerebral hemisphere to the other. The main derivatives of the commissural plate are the following: 1) the anterior commissure, which appears at the end of the embryonic period and later connects the right and the left temporal lobe with each other; 2) the commissure of the fornix, which appears several weeks later and comes to connect the right and the left crus of the fornix with each other; 3) the corpus callosum, which appears early in the foetal period and connects the cerebral hemispheres with each other [12].

The corpus callosum gradually extends considerably in a "front to back" direction and the underlying portion of the commissural plate becomes thinned to form the septum pellucidum [13, 14]. In foetuses both laminae are normally not fused as a kind of physiological CSP. These laminae are supposed to form the vertical SP in the 5th to 6th week of gestational age.

The evaluation of the prevalence of cystic variants of SP in healthy children and adults was the purpose of the present study. The results were derived from high-resolution MRI studies and could be regarded as a kind of baseline information for further studies including patients.

Methods

Subjects

105 healthy volunteers were recruited between 1995 and 2001. We subdivided the subjects into three age groups. The group of young adults includes individuals from 18 to 50 years with a mean age of 31 ± 8 years, the elderly subjects were 59 ± 7 years old. Table 2 shows the age ranges and gender distribution in these three age groups.

All subjects provided a written and signed informed consent prior to the beginning of the study. The volunteers met the following inclusion criteria with negative history of brain injury, drug abuse, or treatment with steroids, tranquilliser medication over the last three months.

Furthermore we included a group of 46 children. The mean age of the children was 6 ± 4 years. The indication for MRI in children was the presumption of diagnosis of inflammatory diseases of brain or tumours with symptoms like unclear headache or emesis. Children under 5 years had to be examined under general anaesthesia and therefore the indication for the examination had to be proven strongly. Informed consent of parents was obtained. By careful analysis of the

Table 2 Characteristics of healthy subjects

	Children	Young adults	Elderly subjects	Total
N	46	72	33	151
Age (years; mean, SD,range)	6±3.9 (0.05–16)	31±8.4 (18–50)	59±7.4 (51–78)	29±20.6 (0.05–78)
Female/Male	23/23	25/47	23/10	71/80

Fig. 1a–c Normal anatomy of septum pellucidum (long arrow). It is attached cranially to the lower surface of the trunk of corpus callosum (short arrow), caudally and posteriorly to the anterior part of the fornix (broken arrow)

images and by clinical follow-up examinations brain tumours or inflammatory brain disease could be excluded. This group of children was accepted as a healthy control group in a previously reported study by the work group of Pfluger et al. [15].

MRI scanning

MR images were obtained with a 1.5 T scanner (Magnetom Vision, Siemens, Germany) using a standard head coil. A vacuum positioning device was employed in order to reduce artefacts by head movements during the measurements.

We acquired a 3D-MPRAGE sequence (TR = 11.6 ms; TE = 4.9 ms; effective slice thickness = 1.5 mm; Matrix: 512x512; FOV 230 mm, 1 acquisition, coronal orientation).

In children these parameters T2- and T1-weighted spin-echo sequences before and after application of Gd-DTPA in weight-related dose were also performed.

The definitions of the variants of septum pellucidum

The septum pellucidum consists of two thin laminae with a potential space between them. Two types of spaces were described: cavum septi pellucidi and cavum vergae.

The corpus callosum defines the anterior, superior and posterior limits of the two cavities which, when not continuous, are separated from each other by the anterior limit of the fornix as it courses obliquely backward and upward from the anterior commissure to the body of the corpus callosum. Being of congenital origin, the two cavities are doubtlessly dependent on the development of the corpus callosum and the fornix. They may coexist and be isolated from each other when the fornix is intact; they may coexist and communicate through a defect in the fornix, or they may form a single large cavity when the fornix is not attached to the corpus callosum. The cavum septi pellucidi is frequently present when the cavum vergae is absent, and Verga's cavity may be present when the cavum septi pellucidi is absent.

Cavum septi pellucidi

The cavum septi pellucidi has the following boundaries: anteriorly, the genu of the corpus callosum; superiorly, the body of the corpus callosum; posteriorly, the anterior limb and pillars of the fornix; inferiorly, the rostrum of the corpus callosum and the anterior commissure; laterally, the layers of the septum pellucidum. On the sagittal images, the cavum septi pellucidi is roughly triangular with the base at the corpus callosum. Viewed in the coronal plane, the cavity is also triangular with its base at the corpus callosum (Fig. 2a–c and 3a).

Cavum vergae

The cavum vergae has the following boundaries: anteriorly, the anterior limb of the fornix, superiorly, the body of the corpus callosum, posteriorly, the splenium of the corpus callosum, inferiorly the hippocampal commissure, the fibres of which bridge the space between the diverging posterior pillars of the fornix. This cavity is also triangular when viewed from lateral. The cavum vergae flares out laterally on both sides with the curve of the fornix and pushes under the lateral ventricles at its extreme lateral extensions (Fig. 3b).

Cavum veli interpositi

The cavum veli interpositi is located in front of the quadrigeminal (superior) cistern above the roof of the third ventricle. It develops as a result of abnormal separation of the limbs of the fornix and is not dependent on the septum pellucidum (Fig. 3c).

Measurements

Two experienced radiologists (C. B., T. F.) evaluated the images separately by using a conventional viewing-station (Radworks 5.0, Marconi, Cleveland, USA). The im-

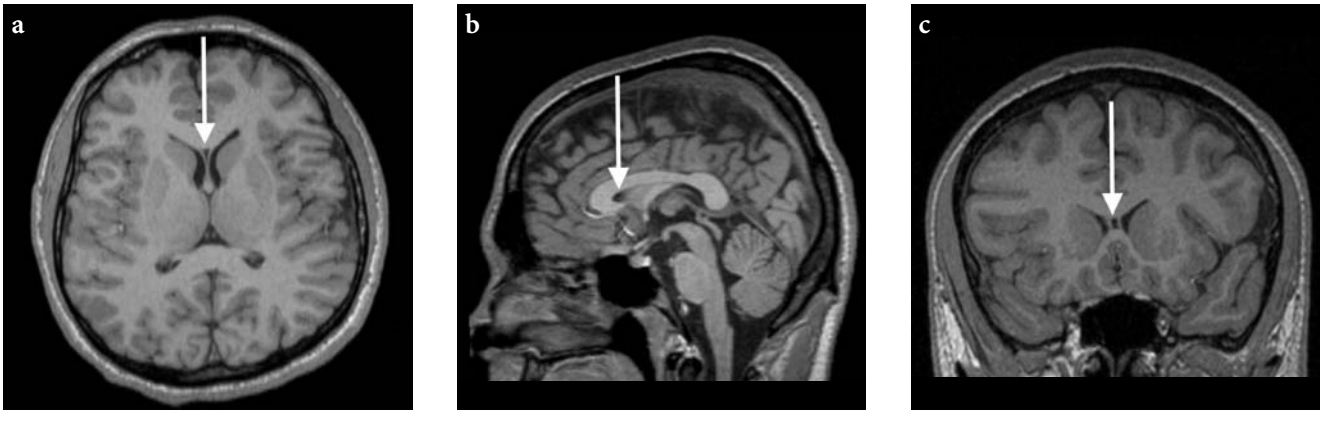

Fig. 2a–c Small cavum septi pellucidi (arrow) in axial (**a**), sagittal (**b**) and coronal (**c**) orientations

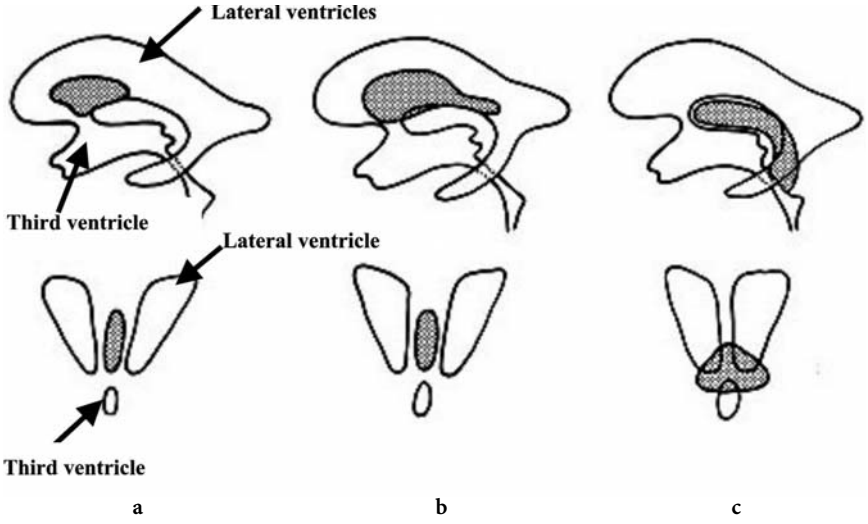

Fig. 3 This scheme considers the midline cavities and their positions in the sagittal and coronal orientation. The grey area illustrates a fluid filled space between the leaflets of SP: **a** CSP, **b** CSP in combination with a CV, **c** cavum veli interpositi

ages were identified by numbers only. Thus the raters were blinded to sex or age.

Reliability for the rating of cava was established on a sample of 50 brains. The interobserver agreement was assessed with an interclass correlation coefficient of 0.88. For ratings with a disagreement, the difference never exceeded more than 2 slices. The differences between the two radiologists were not significant ($p > 0.05$, Mann-Whitney-test). A third radiologists (G. L.) with excellent experience in neuroradiology turned the balance in cases of disagreement.

We evaluated the length of the cava according to the method of Peg C. Nopoulos [16]. Her method entailed a quantitative approach, measuring the size of the cava by its appearance in consecutive coronal 1.5 mm slices: a rating of 1 represents a cavum only seen in one coronal slice, a rating of 2 represents a cavum seen in 2 coronal slices, and so on. With a slice-thickness of 1.5 mm without a gap, the rating reflects the actual anterior-to-posterior length; due to partial volume effects, however, this can only be an approximation. For example a cavum septi pellucidi, with a rating of 5 would be approximately 7.5 mm long.

Fig. 4 MPRAGE sequence (T1-weighted) in coronal orientation (TR/TE 11.6/4.9 ms; eff. slice thickness: 1.5 mm, 512 x 512). This example demonstrates the measurement of the width of cava. The location is the maximum extent of cavum

Classification of findings

Small, triangular formed cava with a size from 1 to 3 slices (1.5 mm to 4.5 mm) were named "variant" type of cavum septi pellucidi. A cavum with a rating of 4 slices, according to 6 mm length, was called a "borderline" type of cavum septi pellucidi.

An enlarged cavum was defined as a cavum with a length of more than 4 slices, according to more than 6 mm in length.

In addition the measurement of the maximal width (in mm) of all cava in coronal slices with an application software (Marconi, Cleveland, US) was performed (Fig. 4). Point of interest was the distance between the leaflets of septum pellucidum. Figs. 4 and 5 demonstrate two examples of CSP with different widths in the coronal plane.

Third, the length of the septum pellucidum was analysed according to the method of rating the cava.

We calculated a ratio using the following formula:

$$\mathrm{Rc} = \frac{\text{length of CSP in mm}}{\text{length of SP in mm}} \times 100$$

Statistics

All statistical analyses were performed by using SPSS version 10.0 (SPSS software, Germany). In the case of deviations from a normal distribution non-parametric

Fig. 5 MPRAGE sequence (T1-weighted) in coronal orientation (TR/TE 11.6/4.9 ms; eff. slice thickness: 1.5 mm, 512 x 512). This example shows a thin space between the two leaflets of the SP

procedures were applied (Mann-Whitney-Wilcoxon test, Kruskal-Wallis test). Paired comparisons were performed by using the Wilcoxon test or Chi^2 tests. On precondition of normal distribution t-test or Anova test was performed. The correlation between succeeding values was evaluated by using the Spearman rank correlation coefficient. A p-value less than 0.05 was considered to indicate statistical significance.

Results

Septum pellucidum

The length of SP was measured in children with 28 ± 6.9 mm, in young adults 35 ± 7.3 mm, in elderly adults 37 ± 5.0 mm (mean, SD). We found a significant difference concerning the length of SP between the children group and the group of young adults (p = 0.001; Anova test) and between the children group and the elderly adults (p = 0.001; Anova test). There was no significant difference between the groups of young and elderly adults (p = 0.431, Anova test).

Cava of septum pellucidum

Table 3 shows the incidences of the CSP in the three age groups. A cavum septi pellucidi was detected in 80.4 % of the children (37/46), in 68.1 % of the young adults (49/72) and in 66.7 % of the elderly individuals (22/33). The difference concerning the existence of CSP between the groups was not significant (p = 0.272, Chi^2 test). In 50.9 % of all subjects, the cava were classified as variant cava septi pellucidi, with a size ranging from 1 to 4.5 mm length. We detected this variant cava in 58.6 % (27/46) of the children's group, in 50 % (36/72) of the young adults and in 42.4 % (14/33) of the elderly persons. Borderline cava with a length of 6 mm were detected in 11.9 % of all individuals. Enlarged cava were seen in 8.7 % (4/46) of the children, in 11.1 % (8/72) of the young persons and in 3 % (1/22) of the elderly individuals. The results showed no significant difference between the age groups (p = 0.364, Chi^2 test).

Both a cavum septi pellucidi and cavum vergae (44/151) were found in 21.1 % of all volunteers. Four of these cases had a continuous form, while both cava were separated in 40 cases. Isolated cavum vergae could be noted in 4 cases of the young adults and in 2 cases of elderly adults.

Over all volunteers variant cava had a mean width of 2.1 ± 0.7 mm; borderline cava 2.8 ± 0.6 mm and enlarged cava septi pellucidi of 8.2 ± 11.0 mm. We could not note a significant difference between the age groups concerning the width of CSP (p = 0.274; Anova test).

Moreover, we could not detect any difference between male and female subjects, concerning the incidences of variants of septum pellucidum (p = 0.423; Chi^2 test).

Ratio Rc

The ratio of the length of the CSP and the length of the SP was 12 % in children, 9 % in young adults and also 9 % in elderly adults (median); however this group showed a smaller area between the 25th and 75th percentile than the young adults. Using the Mann-Whitney test, we calculated a significant difference between the children

Table 3 Incidences of variants of septum pellucidum in three different age groups

Finding	Children N (%) N = 46	Young Adults N (%) N = 72	Elderly Subjects N (%) N = 33	Total N (%) N = 151	P*
Existence of cavum septi pellucidi	37 (80.4)	49 (68.1)	22 (66.7)	108 (71.5)	0.140
Variant; 1.5–4.5 mm	27 (58.6)	36 (50.0)	14 (42.4)	77 (50.9)	0.244
Borderline; 6 mm	6 (13.0)	5 (6.9)	7 (21.2)	18 (11.9)	0.184
Enlarged; > 6 mm	4 (8.7)	8 (11.1)	1 (3.0)	13 (8.6)	0.364
Existence of cavum vergae	10 (21.7)	28 (38.9)	12 (36.4)	50 (33.1)	0.140

* Chi^2 test

group versus the group of young adults ($p = 0.034$) and also between children versus elderly adults ($p = 0.022$), but there was no significant difference between the groups of young and elderly adults ($p = 0.690$, while $p = 0.038$ in Kruskal-Wallis test (Fig. 6)).

Discussion

We conducted a high-resolution magnetic resonance imaging study to evaluate the prevalence of variants of SP in a sample of 151 healthy subjects (HS). The length of SP and the size of the cava were measured by analysing its appearance on consecutive coronal 1.5 mm slices using the method of Nopoulos et al. [16]. In addition, we assessed the width of cava and calculated the percentage of cavum septi pellucidi on septum pellucidum. This method enables an adequate approximation of the size of the CSP using a simple and effective procedure; however the method gives no information about the CSP volume. We detected an overall incidence of cavum septi pellucidi of 71.5 %. Most of these cava (62.8 %) were small, variant or borderline types. Enlarged cava were observed in 8.6 % of all volunteers. The length of septum pellucidum increased with increasing age.

Comparisons with previously reported results are very difficult. The reported prevalence in healthy subjects varies from 2 % to 58.7 % (Table 1; [1, 4, 6, 38, 39]). The wide variance in reported prevalence may be due to several factors, including the method of detection, definition of variants based on size, and inhomogeneity of the populations studied. Such disparity in prevalence may, in part, contribute to the uncertainty regarding the possible pathological implications of CSP.

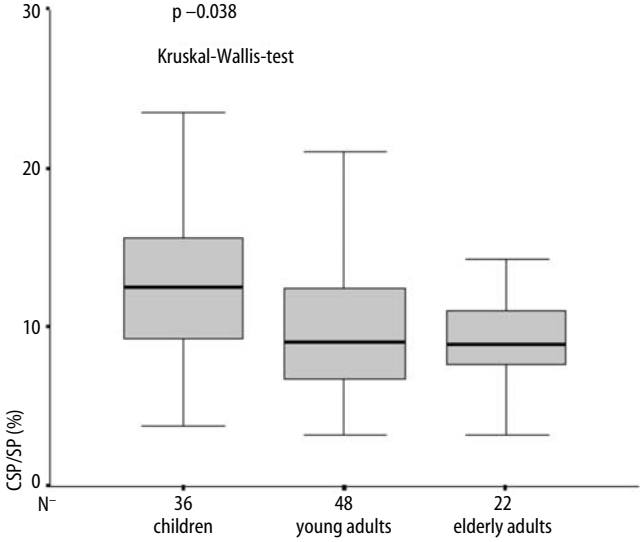

Fig. 6 The ratio length CSP to length SP was noted in children with 13 ± 8 %, in young adults with 11 ± 8 % and in elderly adults with 12 ± 9 % (mean, SD). The figure demonstrates the significant difference between the age groups. The children have a shorter SP and in consequence the ratio is significantly higher; $p = 0.038$ in Kruskal-Wallis test. The black lines in the box illustrate the median. The box itself demonstrates the 25th and 75th percentile. The lines out of the box are the minimum and the maximum

It is well known that small cava septi pellucidi are common in large populations of healthy subjects [39–42]. In 1997, Nopoulos et al. reported an incidence of cavum septi pellucidi (including all sizes) in 75 healthy adults of 58.7 % and in a patient group (schizophrenic disorders) of 58.5 %. The population of Nopoulos et al. had a mean age of 27 ± 7.8 years. The scanning technique and the rating scale was comparable with our own study. In her study, enlarged cava septi pellucidi were rated in 1.3 % of controls and in 21 % of psychiatric patients [43]. In comparison, we detected small, variant and borderline sized cava in 67 % of the adults and enlarged cava in 8.6 % of the adults. The difference between the incidences may be a result of inhomogeneity of the population.

In a second study, Nopoulos and her colleagues included 95 healthy children with a mean age of 11 years. The main topic of this study was the comparison between healthy individuals and patients suffering from early onset schizophrenia. The authors reported an enlarged CSP in 1 of 95 (1.1 %) healthy children. 3/24 (12.5 %) schizophrenic patients with a mean age of 14 years had an enlarged CSP. Using a similar method, we detected a rate of enlarged CSP of 8.7 % in healthy children.

The studies of Degreef, Jurjus and Scott used a qualitative rating scale for evaluation of CSP (0 = absent; 1 = equivocal, 2 = small, > 3 = moderate to large). Objective measurements of size of cava were absent. Degreef's study included only grades 2 and above to assess the presence of CSP and reported incidences of 2 % [4, 5]. Degreef performed sequences with a slice thickness of 3.1 mm without a gap. Jurjus et al. described incidences of 19 % in normal controls and of 25.4 % in schizophrenic patients [38]. Scott et al. noted an incidence of 5 % in neurological patients. These work groups used a scanning protocol with an effective slice thickness of 5 mm. Due to this fact, small cava may have remained undetected.

Furthermore, some studies have indicated that the incidence of cavum septi pellucidi is higher in male compared to female subjects [38, 44, 45]. Nopoulos et al. noted incidences of all sizes of CSP in males of 67 %, which was significantly higher than that found in females (46 %). We could not confirm these results. In our population there was no difference of incidences of CSP between males and females.

Many studies indicated that neurodevelopmental disturbances may play an important role in the pathogenesis of psychotic disorders or mental retardation [17–20, 25, 26]. Developmental brain anomalies associated with schizophrenia included corpus callosum dysgenesis [1, 2, 21], grey matter heterotopia [22] and ventricular enlargement [23, 24]. In addition, there were several studies reporting an increased incidence of an enlarged cavum septi pellucidi in patients with schizophrenia [1, 4–7]. It has been speculated that an enlarged cavum septi pellucidi represents a form fruste of mid-line abnormalities, a marker for limbic system dysgenesis, or both [32, 33]. In addition, an enlarged cavum septi pel-

lucidi has been reported to be associated with cognitive deficit in developmental disorders such as mental retardation [33] or Apert's syndrome [35].

Considering the embryological facts, a septum pellucidum could not be existent without the development of corpus callosum. Agenesis of corpus callosum is always associated with the agenesis of septum pellucidum. Absence of the septum pellucidum can provide a valuable clue to the diagnosis of holoprosencephaly, agenesis of corpus callosum, chronic severe hydrocephalus, basilar encephaloceles, porencephaly and the septo-optical dysplasia [35, 36]. Whether an isolated absence of the septum pellucidum really exists is in discussion. Supprian reported of two cases of an isolated absence of septum pellucidum; one patient presented a schizophrenic psychosis [37]. Barkovich had never observed an absence of the septum pellucidum without associated malformations [36].

The normal brain maturation, in which the two leaflets of the septum pellucidum were fused, is directly related to the rapid growth of hippocampal alvei and the corpus callosum [46]. Associations between hippocampal malformations and the appearance of schizophrenia were also described [47, 48]. This suggests that dysgenesis of either the hippocampus or corpus callosum could possibly lead to an arrest of the fusion process, causing a larger than normal cavum septi pellucidi to persist into adult life. In most, if not all, foetuses, the two leaflets of septum pellucidum are separated by a cavity of varying size [30, 49]. This cavity begins to disappear before birth, but it could be seen in about 80 % of infants at term. The cavum septi pellucidi usually shrinks and disappears long before adulthood [30]. Spontaneous regressions of CSP were reported previously of Kocer et al. [50]. Our results support the hypothesis that cavum septi pellucidi disappears very early in childhood. Even if a subgroup analysis does not allow for a statistical evaluation, a tendency of high incidences of CSP in young infants could be presumed.

In the present study the overall incidence of cavum vergae was 33 %. In the majority of the subjects (29 %), cavum vergae was combined with cavum septi pellucidi, but both cava were separated. Just four cases had a continuous form of separation of the two leaflets of the septum pellucidum. Cavum vergae was described in 30 % of normal adults by de Lisi et al. [6], comparable with our results. However, there is a considerable disagreement in the literature about the incidence of cavum vergae in normal subjects [30, 41, 49, 51]. In our opinion, this disagreement may be a problem in the definition of cavum vergae. The frequently used definition in textbooks is that cavum vergae is a fluid-filled space between the two leaflets of septum pellucidum in its posterior part. Most examples show a space between the crura of the fornix and below the commissura hippocampi. However this is the space of velum interpositi. There is no anatomical association to septum pellucidum. This space has a connection to the third ventricle. High-resolution imaging makes it possible to visualise the difference between the thin structure of the septum pellucidum and the thickened crura.

An increased incidence of cavum vergae in newborns was reported by Rauschning, who found a cavum vergae in 80 % of newborn infants and in 26 % of healthy adults [25]. Nakano et al. reported a gradually decreasing incidence of both cavum septi pellucidi and cavum vergae. He reported an incidence of 10 % in 1 year old children, 6 % in 2 to 5 year old children, 3 % in 6 to 9 year old children and 2 % in 10–14 year old children with an average rate of 5.5 % [52]. These results were obtained in CT scans and, therefore, they are not comparable with our results. The results of our study could not confirm higher incidences of cavum vergae in children. The MRI study of Aldur et al. described that cava vergae were very frequent in the group of 0 to 9 year old children [53]. Oteruleo reported that a cavum vergae never occurred without a cavum septi pellucidi [54]. Auer et al., however, found this form of cavity in a postmortem study. We found an isolated form of cavum vergae in 4 % of all healthy individuals.

Conclusion

In a large healthy population there is an incidence of CSP, including all sizes, of 72 %, so-called enlarged CSP were seen in 9 %. We noted no dependency on age or gender.

The incidence of CV was 33 % (29 % in combination with cavum septi pellucidi, 4 % isolated cavum vergae). No age-dependency was found.

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