# The quest of cavum septi pellucidi: obscure chance event discovery or the result of some encoded disturbance ?

Developmental cerebral dysplasias, cavum septi pellucidi and epilepsy: clinical, MRI and electrophysiological study

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**Abstract**

**OBJECTIVES**: Developmental cerebral dysplasias are frequent causes of epilepsy. The early stage of gestation, mainly the period of neural crest separation and neuroblast migration (disturbance of midline structures, heterotopias, cortical dysplasias and disturbance of the ventricular and vascular formation), may be considered as a cause of serious cerebral dysplasia. The aim of the study was focused on frequent simultaneous occurrences of epileptic seizures and the defect or abnormality of the ventricular system – cavum septi pellucidi (CSP).

**MATERIAL AND METHOD**: In our study the clinical symptoms, EEG and somatosensory evoked potentials (SEP's) following median nerve stimulation and MRI pictures in the group of patients with CSP (n= 35), were analyzed. In the SEP analysis, a control group of normal, healthy volunteers (n = 40) and a group of age matched patients with epileptic seizures of different origin, without structural lesions evident on MRI (n=21), were used.

**RESULTS**: Analysis of the patient population with CSP (CSP was confirmed by MRI) showed that approximately in 2/3 cases, different types of cranio-cerebral dysplasias were evident on MRI. More than 2/3 of the patients with CSP showed epilepsy and an abnormal EEG record, however, focal EEG changes were seen more frequently in the group of patients with epilepsy without CSP, than in patients with CSP. The SEP's in patients with CSP showed a statistically significant prolongation of latency of thalamic P15 waves, however these changes were not present in the group of patients with epilepsy of a different origin.

**CONCLUSIONS**: In a group of patients with CSP, dysplastic MRI changes, together with the prolongation of thalamic wave latencies according SEP, were examined. These clinical symptoms may be considered the result of disturbances of early gestation and of lesions of midline structures. CSP became an interesting model opportunity for us, and allowed for the clinical, MRI and electrophysiological examination of developmental cerebral dysplasias. We believe that there is an important role for septal and diencephalic midline structures in cerebral electrogenesis, and possibly in the origin of epileptic seizures too.

ORIGINAL ARTICLE

## Introduction

The views on the importance of absence, hypoplasia or other dysplastic changes of septum pellucidum are very different. Williams et al. (1993) think that aplasia or absence septum pellucidum is a clinically insignificant finding [15]. Aicardi in 1981 described the syndrome of absence septum pellucidum with porencephalias and other developmental defects, and previously De Morsiere (1956) described the syndrome, which is well known as septo-optico- pituitary dysplasia and which is considered a very important developmental disturbance [1, 13].

The syndrome of septo-optico-pituitary dysplasia is well characterized: less than 40% of cases have optic nerve or chiasma hypoplasia, the absence or hypoplasia septum pellucidum (SP) is also usually present in less than 40% of cases, and in 2/3 of the cases there may be a disturbance of pituitary dysfunction (hyposecretion of GSH and TSH); however, this clinical syndrome, as a complete triad, is very rarely present [12]. The discovery of another developmental disturbance is very important, namely heterotopias and schisencephaly. [6, 10]

Anatomically, SP is the midline structure, which consists of two vertically oriented sheets, and septum verum is present on both sides, which consists of nervous tissue – as the borderline nuclei septi pellucidi are confined or limited. The ceiling on the upper side is the corpus callosum, while below are the commissura anterior, Broca´s fasciculus and optic chiasma present (fig. 1). Functionally the structures of SP have an intimate relationship to commissural pathways, and via septal nuclei, to other parts of the limbic and diencephalic system (hypothalamo-pituitary and thalamic system or more generally to mesodiencephalic structures).

The causes of this syndrome are most frequently attributed to developmental disturbances (genetically or non-genetically determined), because evidence does exist that suggests the cause may be con-genital such as a cytomegalovirus infection, or other toxic influences (some drugs or fetal alcoholic syndrome) [3, 9].

The role of cavum septi pellucidi (CSP) is obscure, and equally unknown is the role of CSP in the pathogenesis of the epileptic seizures, in which 2/3 of cases, CSP was found.

Therefore, we felt that it was important to analyze this clinical-electrophysiological phenomenon; the presence of epilepsy and the simultaneous presence of cystical formation localized in the septum pellucidum along with some other possible developmental disturbances in MRI features.

The main problem and aim of this study was to address the following questions:

1. Was CSP a component of developmental dysplasia of midline structures classified and accepted?
2. Could we accept the role of EEG and somatosensory evoked potentials (SEP's) as evidence for the identification of a silent midline structural lesion?
3. Does there exist the possibility of some causal continuity between the presence of CSP and epileptic seizures?

## Material and methods

In our clinical register, in a five-year period, we were able to gather 35 cases in which CSP was confirmed by MRI examination. The patient population was between 16 and 36 years of age. We compared this group with a group of patients of similar age who had different types of epileptic seizures that continued after childhood or adolescence (n=21). All patients with epilepsy were completely examined clinically (MRI inclusive) and they did not have any apparent focal cerebral lesion. As a control we used a group of healthy individuals aged 16–40 (n=40). In addition to clinical neurological examinations, a classic EEG examination was performed (with activation
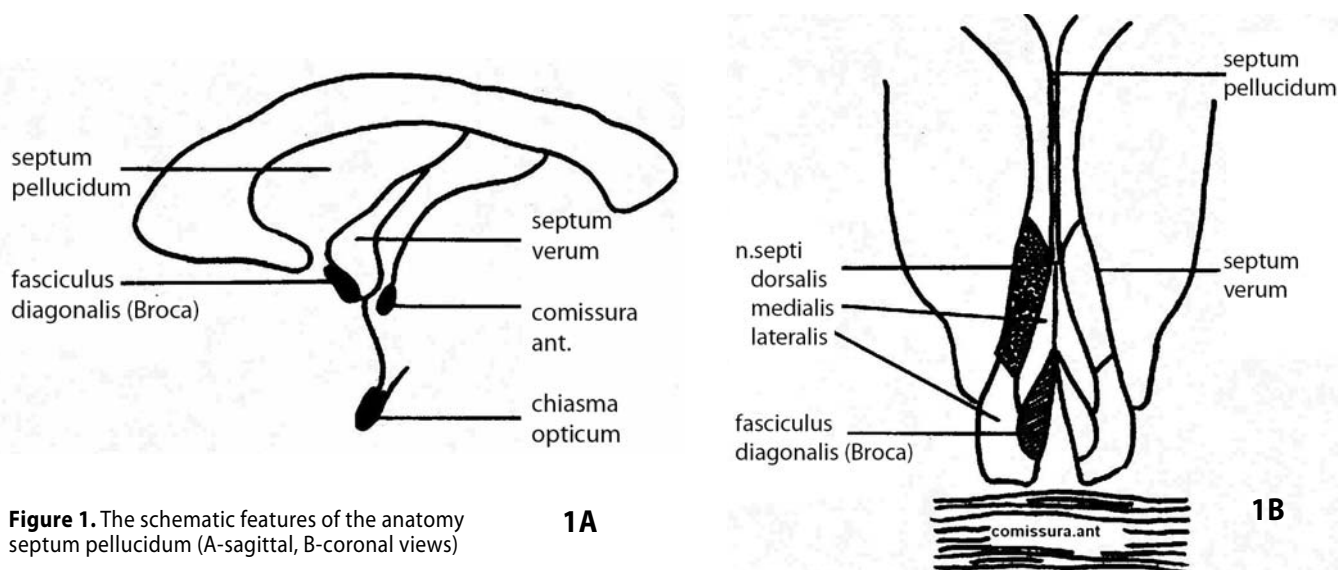


**Figure 1.** The schematic features of the anatomy septum pellucidum (A-sagittal, B-coronal views)

**1A**

**1B**

by hyperventilation, photostimulation and EEG following sleep deprivation and in the majority of cases LTM-EEG).

Evaluation of somatosensory cerebral function by SEP examination was done. SEP examination was performed on Medelec-92 equipment. Stimulating electrodes were placed on the wrists using bipolar electrodes. The median nerve was stimulated by square pulses. The time frame for cortical SEP recordings was set at 100 ms and 50 ms was used for spinal recordings. Each record consisted of 1024 average responses and it was repeated at least twice. Cortical recording electrodes were placed on the scalp at C3 and C4 locations according to 10–20 system. SEP's from contralateral cortical C3 and C4 electrodes after median nerve stimulation were recorded. For spinal recordings, active electrodes were placed over the spinal processus CV5 and the reference electrode was placed on the ear lobe. To assure the accuracy of our methodology and sound technical equipment function, we repeated studies of the same patients five times during a five-day period under identical testing conditions and procedures [4, 5]. The configuration and consistency of these recordings was very stable.

The analysis of singular latencies and amplitudes were done according to T-test protocols (Table 1).

## Results

1. The incidence of cerebral dysplasias (heterotopias, cortical dysplasia and the abnormality of ventricular system – asymmetry or hydrocephalus) in the group of patients with CSP was confirmed in 70% of the group, and in 33.3% of the group of epileptics respectively.
2. Epileptic seizures in the CSP group were found in 57,1% (more frequently focal than secondary and primary generalized seizures). Table 1.
3. More than 2/3 (68,6%) of the patients with CSP had an abnormal EEG; and most frequently non-focal epileptiform abnormalities (42,9%) were found. In contrast, in the group of epileptic patients, an abnormal EEG record was evident in 76,9% and non-focal was present only in 19,8%. These findings are compatible with the type of seizure and the number of patients with primary and secondary generalized seizures.
4. In SEP examination, the statistically significant delay latency of the P 15 wave ($p < 0,01$) in patients with diagnosed CSP, and in both groups the increase of the amplitude P 25 waves, were found.

## Discussion

The normal development of the human brain depends on the normal structure of genetic material and on the elimination of negative pathoplastic influences during the initial stages of gestation. All serious cerebral dysgenetic defects are generated before the 9th or 10th week of the gestation. After this period, proliferation and differentiation precursors cells in the ventricular zone generate many immature neurons that leave the ventricular zone in two waves of the migration: the first is in 10th and the second in 13th to 15th weeks of gestation [6].

**Table 1.** The symptoms of clinical and MRI picture and EEG findings in a group of healthy volunteers (n= 40), patients with CSP (n= 35), and in a group of epileptics (n= 21).

| Group of Patients | Normal n = 40 | CSP n = 35 | Epilepsy n = 21 |
|---|---|---|---|
| **Clinical Symptoms** | | | |
| ▪ sensitive | – | – | – |
| ▪ motoric | – | – | – |
| ▪ epilepsy (type) | – | 20 (57.1%) | 21 (100%) |
| – focal | – | 12 (34.3%) | 16 (76.1%) |
| – non-focal | – | 8 (22.8%) | 5 (23.9%) |
| ▪ mental retardation | – | 6 (21%) | 2 (4.2%) |
| **Somatic Disturbance** | | | |
| ▪ facial | – | – | – |
| ▪ skeletal – short stature | – | 6 (21%) | – |
| ▪ endocrine | – | 1 (3.5%) | – |
| **EEG** | | | |
| ▪ normal | 40 (100%) | 11 (31.4%) | 5 (23.1%) |
| ▪ focal | – | 9 (25.7%) | 12 (57.1%) |
| ▪ non-focal | – | 15 (42.9%) | 4 (19.8%) |
| **MRI** | | | |
| ▪ SEH | – | 5 (17.5%) | – |
| ▪ CD | – | 1 (3.5%) | – |
| ▪ AVS + H | – | 14 (49%) | 7 (33.33%) |
| ▪ CSP | – | 35 (100%) | – |

SHE – subependymal heterotopia, CD – cortical dysplasia,
AVS + H – abnormalities of the ventricular system + hydrocephalus
CSP – cavum septi pellucidi

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| SEP | | Control (n=40) | | CSP (n=35) | | EPI (n=21) | |
|---|---|---|---|---|---|---|---|
| C3/C4 | (side) | L | R | L | R | L | R |
| | | | | ** | ** | | |
| P15 | L | 16.2 ± 0.4 | 16.0 ± 0.4 | 17.2 ± 1.5 | 18.5 ± 3.5 | 16.0 ± 1.5 | 17.0 ± 3.0 |
| | A | 2.0 ± 0.7 | 2.0 ± 0.4 | 2.0 ± 1.0 | 1.8 ± 0.4 | 1.8 ± 1.5 | 2.2 ± 1.0 |
| N20 | L | 21.7 ± 4.2 | 21.4 ± 2.0 | 21.8 ± 2.5 | 23.0 ± 2.5 | 20.6 ± 4.0 | 21.0 ± 3.8 |
| | A | 1.4 ± 1.5 | 0.8 ± 0.4 | 1.0 ± 1.2 | 1.2 ± 1.1 | 1.8 ± 1.2 | 1.8 ± 1.1 |
| N 25 | L | 26.3 ± 5.0 | 28.0 ± 2.5 | 28.0 ± 4.0 | 29.5 ± 5.0 | 28.0 ± 3.5 | 27.5 ± 6.0 |
| | | | | ** | ** | | |
| | A | 1.7 ± 1.1 | 3.0 ± 0.8 | 4.4 ± 2.2 | 4.8 ± 2.4 | 3.5 ± 1.5 | 3.5 ± 1.2 |

**Table 2.** The values of the SEP registered from electrodes C3/C4 after contralateral median nerve stimulation (* – $p$ 0.05 , ** – $p$ 0.01)
L-latencies, A- amplitudes

For many years, most cerebral and cortical malformations of development were recognized only post mortem and so considered to be rare (prevalence 11.2 per million births) and no data for cortical dysplasias, heterotopias or another malformations were available [6]. Recently, neuroimaging studies in populations have suggested that cerebral developmental dysplasias are more common than was previously appreciated. They appear to be a very important factor in the etiopathogenesis of epilepsy and developmental delay in children.

Neural crest separation, and neuroepithelial cell proliferation and differentiation are the periods with important influence on cerebral dysplastic formation.

As the neuroectoderm develops in the epiblast at 3 weeks postovulation in humans, it becomes organized as a pseudostratified columnar epithelium – a sheet of bipolar cells oriented so that one cytoplasmic process extends to the dorsal (future ventricular) surface and the other process extends to the ventral (future pial) surface. This population of quiescent neuroepithelial stem cells in the ependyme of the subventricular region of the forebrain retains a proliferative potential for gliogenesis, and perhaps for neurons, even in adults too. The floor plate is the first structure of neuroepithelium to differentiate [14].

In general, great attention is dedicated to cortical development, very frequently described as "neuronal migration disorders," which is connected with abnormal cell formation in the ventricular zone and which precedes the period of neuroblast migration.

The main problem of this study about the genesis of CSP was the question of whether or not the presence this abnormality is the result of some developmental disturbance.

In ½ of the cases with CSP, the abnormal configuration of the ventricular system (hydrocephalus, ventricular asymmetry) was present and in 1/5 of the cases disturbances in neuronal migration was also evident. We assume and accept that these findings are sufficient evidence for the confirmation of a developmental disturbance of different origin.

The next problem and question was the clinical and electrophysiological confirmation of a silent or unapparent lesion of midline structures of the brain.

More than 2/3 of the patients with CSP epilepsy showed an abnormal EEG record (more than 40% with non-focal disturbances of electrical activity).

This finding was what motivated and led us to conduct electrophysiological examinations and testing of the afferent system by the method of SEP. We assumed that changes of SEP's give us some answers about the conductive processes and the generation of electrical activity in some structures of the CNS [4, 5, 15]. In the group of patients with CSP we found a delay in latency of thalamic P15 wave and the increased amplitude of the P25 wave. The P15 wave is considered a generator of electrical activity in thalamic nuclei and the N20 and P25 waves as the primary cortical response.

In conformity with these findings is the more frequent incidence of primary and secondary generalized seizures and non-focal epileptiform changes in the EEG's in a group of patient's with CSP. The change in latency of the P15 wave is specific to the group of patients with CSP. It can give evidence about the damage of the mesodiencephalic system in relation to the midline structural lesion in CSP.

The presence of clinical symptoms of pituitary dysfunction in approximately 20% of the patients was seen (short stature and in 1 case Froehlich´s syndrome), which is more than in normal healthy populations, hence we may accept the confirmation of pituitary dysfunction.

The problem of the pathogenesis and causes of epileptic seizures has not been clearly defined. Epileptic seizures could originate or could be provoked by many factors, which could have an influence on the synchronization and modulation of brain electrical activity. It seems that those factors which are responsible for the origin or propagation of the electrical discharge are found equally in centrencephalic as well as in telencephalic structures, although the frontal and temporal lobes are the most frequent source of the clinical and electrophysiological epileptogenic manifestations.

The most sensitive are the limbic system, diencephalo (thalamo)-temporal or septo-hippocampal system and the frontal lobe. Wyllie (1997) considers macro and microscopic changes in this region to be the most frequent cause of epileptic seizures [17]. Our attention was focused on the frequent association of epi-
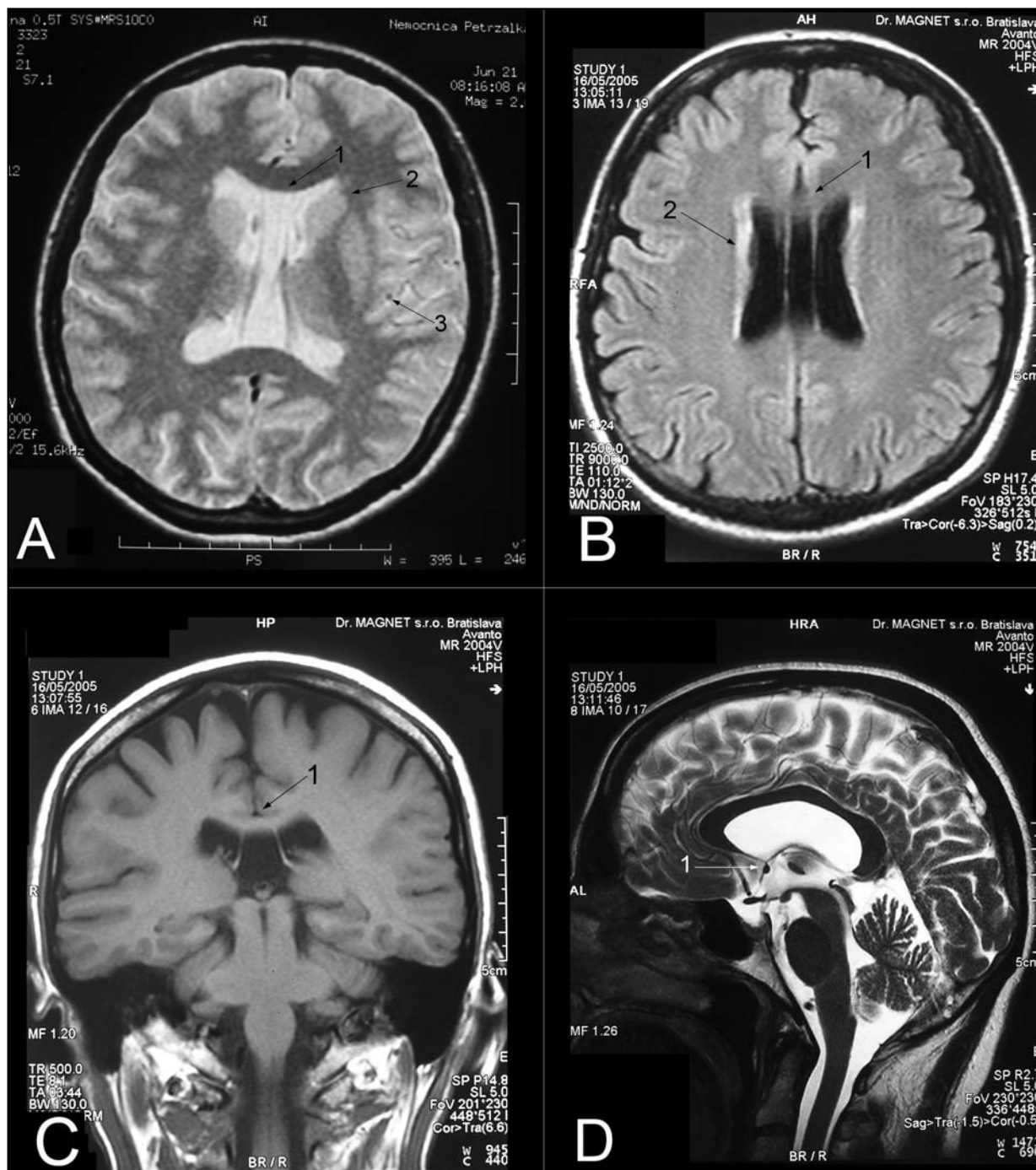
**Figure 2.** 36 year old woman with epilepsy from 15 years: two axial MRI scans in T2W MRI after contrast medium (A)and T1W MRI (B) (1– CSP, 2– SEH, 3– "double cortex " and wide Sylvian groove), coronal scan in T1W MRI (C) and sagital scan in T2W MRI (D)

leptic seizures with the presence of CSP. Kuriyama et al. (1998), and Wyllie (1997) describe septooptical and optico-septal- pituitary (or diencephalic) dysplasias as one of the most frequent causes of epilepsy in childhood and dolescence [11, 17].

Aicardi(1986) states that 25% of epileptic seizures experienced in childhood and adolescence have their onset during prenatal development, 15% during perinatal and the rest during the postnatal period of the development [2]. The etiology of these epileptic seizures is most often classified as unknown.

We have not found any mention about CSP as a source of epileptic seizures in the literature. Microscopic lesions are frequently not detectable with 'imaging methods' or even in necropsy, hence they are generally not identified. But in some cases, in cortico-subcortical structures of the forebrain together with CSP, other developmental abnormalities (as the cause of epileptic seizures) are frequently discovered and confirmed.

From this point of view, CSP may be classified as a defect of midline structures of the brain (dysraphic defects), which may either occur in genetic binding

on the X chromosome or sporadically. Frequent data about other developmental MRI symptoms in a group of patients with CSP raise two questions:

1. Is CSP only a solitary symptom of the abortive cerebral developmental disturbance or is only one part of complex combined developmental changes of midline structure and lissencephaly? fig. 2
2. Is the presence of CSP an equally important factor for midline lesion similarly as aplasia or hypoplasia SP and may be as developmental dysplasia considered?

The MRI and SEP findings in patients with CSP suggested that in some cases there is a cortical developmental disturbance (neuroblast migration) together with a disturbance of ventricular system formation (hydrocephalus, ventricular asymmetry and CSP) and with a disturbance of diencephalic and brain stem structures. The cause of this clinical picture may be the changes in the early period of gestation between 4th and 13th weeks of gestation, when the neural crest, marginal and ventricular zone formation is initiated and the proliferation, differentiation and neuroblast migration continually proceeds.

Thus microdysplastic cortical lesions are also very frequently present, whose presence may be only questionably or even never may be confirmed, and which act as epileptogenic foci. Its spread by two main mechanisms are further considered: as a direct lesion or as a process of differentiation of some part of the cortico-subcortical cerebral structures [7, 8].

In the process of epileptogenesis the forebrain plays a more important role than the back part of the brain; namely the orbito-septo-hippocampal and mesodiencephalo-limbic systems play a key role in epileptogenesis. If CSP is present, then this abnormality, as a space occupying formation, compresses the tissue of the septum verum (with the septal nuclei) against medial wall of lateral ventricles and thus may be the source of the lesion of septo-hippocampal pathways.

Finally we want note that cystic formation in midline became an interesting model opportunity and experience for clinical and electrophysiological research in the electrogenesis of epileptic seizures. This finding of CSP may be one from the visible signals of the developmental cerebral dysplasias.

## Conclusion

1. CSP may be considered as a local developmental defect in the cerebral midline structures with a possible relationship to the midline optico-septo- pituitary (diencephalic) dysplasias.
2. In the group of patients with CSP (n=35) in 70%, other different developmental cerebral defects by MRI were seen, epilepsy was observed in 57.1% of cases, and in 68.6% of the patients, an abnormal EEG (more frequently non- focal) was seen.
3. The most important change in the SEP was the latency prolongation of the thalamic P15 wave in the

group of patients with CSP. This phenomenon may be related to the functional and clinically unapparent disturbance of the diencephalic system in CSP.

We consider all of these findings extremely interesting, however their origin is not clearly explained and still remains obscure.

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