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RESEARCH ARTICLE

CYST OF SEPTUM PELLUCIDUM IN MENTAL DISORDERS: SCHIZOPHRENIA AND MENTAL RETARDATION: TWO CASEREPORTS

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Abstract

A septum pellucidum cyst is defined as a fluid collection between the lateral ventricles whose walls have a lateral curvature and are separated by 10 mm or more . Most of these cysts are benign and their clinical significance should be considered as a neurodevelopmental anomaly that may contribute to neuropsychiatric abnormalities . It is often of incidental finding, of little clinical significance. However, an association between this developmental anomaly and a mental disorder, such as schizophrenia and/or intellectual disability, has been reported. We report in this study two clinical cases, diagnosed with schizophrenia comorbid with intellectual disability and in whom brain imaging has objectified a cyst of the septum pellucidum. The objective of this study is to discuss the relationship between the septum pellucidum cyst and mental disorders, especially schizophrenia and intellectual disability.

Introduction:-

The septum pellucidum (SP) is a thin membrane that separates the anterior horns of the lateral ventricles.

Cavum Septum Pellucidum (SP), cavum vergae (CV), and cavum interpositum (CVI) are the anterior midline intracranial cysts most often described. Cavum of the SP is a cavity located between the membranes of the SeptiPellucidi. The CV is an extension of SP, located posterior to an arbitrary vertical plane formed by the columns of the fornix. CVI is a true cistern situated above the third ventricle. Most of these fluid collections are benign and considered a normal anatomical variant, but sometimes they become symptomatic and require surgical treatment.

The pathogenesis, the mechanism for cyst expansion, and risk factors are not fully understood. A cyst of septum pellucidum (CSP) can obstruct the interventricular foramina and compress the structures of the hypothalamic septal triangle as well as optic pathways causing intracranial hypertension, visual, behavioral, autonomic, and sensorimotor symptoms.

Since 1851 there have been numerous single case reports and small case series linking various types of psychoses including schizophrenia with abnormalities of the Septum Pellucidum; Furthermore, several studies have established that enlarged CSP is associated with schizophrenia and maybe considered a marker for cerebral maldevelopment.

Also enlarged CSP has been associated with cognitive dysfunction in heterogeneous pediatric groups showing neurologic abnormalities, mental retardation, and developmental delay.

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To date, schizophrenia probably remains to be the most challenging neuropsychiatric disease to both neuroanatomists and neuropathologists.In fact, morphological brain changes have long been noted in schizophrenia, although it is unclear whether they are a consequence of an early disturbance in brain growth or represent a deterioration from what once was normal brain structure. If a marker of brain developmental disturbance were found to be associated with schizophrenia, even though the underlying defect were not detected, this would lend support for a general neurodevelopmental hypothesis.

In this case study, we describe two patients with schizophrenia and mental retardation who were found to have cyst of septum pellucidum on brain imaging.

Case Reports:

Case1:

A 37-year-old male was admitted to the psychiatric emergency department for agitation and heteroaggressive behavior.His symptomatology seems to go back to 2002, at 17 years old, when he first presented negative symptoms, such as isolation and social withdrawal. The patient consequently developed delusional thoughts of persecution toward his neighbors. Also, he presented many suicidal thoughts/attempts in response to unfamiliar voices that urge him to harm himself.He had several psychiatric consultations and was put on different antipsychotics for sufficient doses and durations but without any significant improvement. in 2016, he was hospitalized in intensive care for attempted suicide by drug ingestion.

The worsening and the lack of improvement of the state of the patient due to his drug-resistant schizophrenia required his admission to the hospital for better management and clinical care.

Past history revealed no other diseases besides his previously diagnosed schizophrenia and past psychiatric management, yet he had no past history of seizure activity, incontinence, head trauma, drug or toxin exposure . Family history of the patient was negative for schizophrenia or other mental diseases. He had had a normal delivery yet had experienced a psychomotor delay and suffered from a stuttering that has persisted to this day. He had dropped out of primary school after several failures and never received further education or worked following his drop-out;the diagnosis of moderate mental retardation was subsequently made.

Examination revealed an alert male in no distress. His general neurological examination was unremarkable. He was calm,fully oriented.His speech was marked by a stuttering, His thought content was remarkable for delusional thoughts of persecution toward his neighbors, he reported auditory hallucinations consisting of abnormal voices, not known to him, urging him to harm himself, and a mental automatism. His affect was blunted, but his subjective mood was normal. his insight was negative.

All laboratory studies, including electrolytes, thyroid function tests, liver function tests, kidney function tests, tests for syphilis, serologic tests for HIV, HBV, HCV, urinalysis, and drug screen, were normal. An EKG on testing was also normal.

On neurological testing, an electroencephalogram showed no anomalies. A CT scan of the head found no anomalies of the brain structures but revealed, however, a cyst of the septum pellucidum.

Organic causes were ruled out and he met Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Revised (DSM-5-R) criteria for schizophrenia.

In view of his treatment-resistant schizophrenia, and after eliminating a contraindication to treatment, he was given clozapine with a gradual increase in dosage and biological control of the complete blood count (CBC). At 600 mg/day, a clear clinical improvement was observed with remoteness of his delusions of persecution and regression of auditory hallucinations.

Case 2:

A 21-year-old female was admitted to the psychiatric emergency department for agitation and behavioral disorder. Her symptomatology seems to go back to age of 15, when she developed symptoms of anhedonia and social withdrawal. She was first diagnosed with a depressive disorder for which she was put on antidepressants medications with no significant improvement. Then she presented delusional thoughts of persecution toward her

father, who, according to her, was plotting against her. She reported that she usually found publications in social media in which unknown people talked about her. In spite of her mental state, she did not consult and did not benefit from any therapeutic management.

For about a month, her mental state worsened, she became irritable, had several fits of agitation, became aggressive and very persecuted against her father.

Her past medical history was notable for psychiatric management of depression following an attempted suicide by phlebotomy,there was no history of head trauma or seizures. Family history was negative for mental diseases, but revealed, however, a sibling with trisomy-13 syndrome, motor deficit, and cardiac malformation.

She had had a normal birth and delivery. Her developmental milestones were normal. She has been a victim of bullying and abuse from her classmates at an early age, due to her hands' tremor and stuttering, which led to her dropping out of high school.

Examination revealed an alert female in no distress. Her general physical examination revealed phlebotomy scars on the anterior face of the forearm and bilateral tremor of both hands. She was agitated and aggressive, fully oriented, her speech was full of obscenity, her thought content was remarkable for delusional thoughts of persecution against her father, and mystical. She reported auditory hallucinations and ideas of reference.

To note that her responses and behavior were marked by an immaturity

Her affect was blunted, but her subjective mood was normal. Further psychiatric interviews objectified a negative insight, disturbed sleep and judgment, a loss of appetite.

All laboratory studies, including electrolytes, thyroid function tests, liver function tests, kidney function tests, serologic tests for syphilis, HIV, HBV, HCV, urinalysis, and drug screen, were normal. An EKG on testing was also normal.

On neurological testing, an electroencephalogram showed no anomalies. A CT scan of the head found no anomalies of the brain structures but revealed, however, a cyst of the septum pellucidum.

Organic causes were ruled out and she met Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Revised (DSM-5-R) criteria for schizophrenia and mental retardation.

She was given olanzapine (20 mg/day) and a clear clinical improvement was observed afterwards with remoteness of her delusions of persecution and regression of auditory hallucinations.

Discussion:-

The septum pellucidum is a brain midline structure comprising two translucent parallel membranes. Three types of midline abnormalities involve the SP: cavum septum pellucidum (CaSep) (which is the anomaly found in our case study), cavum vergae (CaV), and cavum velum interpositum (CaVI); They are easily identifiable by either CT or MRI scanning.

Abnormally, failure of the fusion of the two membranes leads to the occurrence of cavum septum pellucidum (CSP). In more than 85% of cases, the CSP fuses by three to six months of life. Its prevalence sharply declines soon after delivery, such that it is 85% at one month, 45% at two months, and 15% at three to six months. It closes in a caudal to rostral fashion, resulting in obliteration of the caudal portion first (at 38 weeks of gestation).The anterior portion only obliterates by three to six months of age, which occurs due to the rapid growth of the corpus callosum and hippocampal alvei along with the concrescence of cerebral hemispheres leading to the fusion of the membranes of SP.

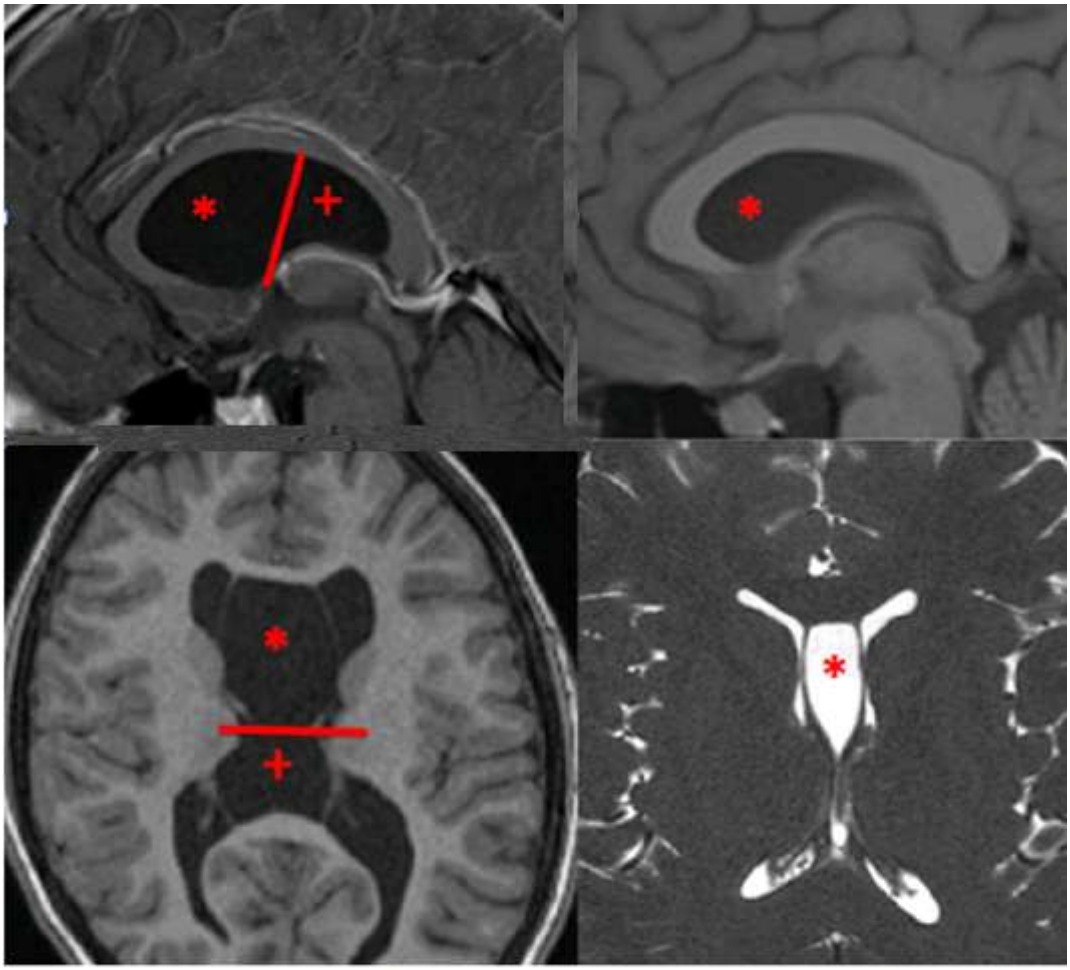

Fig. Image of cysts of CSP (*) and CV (+). Borderline between CSP and CV is marked by red line

Many previous studies have suggested that, as a potential neurodevelopmental marker, CSP plays a role in the genesis of mental disorders. Septum pellucidum is more than just a neural tract that connects the corpus callosum and fornix in spite of the misconception that the septum pellucidum has no function (based on the poor understanding of its embryology and connections). It is a component of the limbic system that acts as a relay station to the main hippocampal and hypothalamic nuclei, as is evidenced by symptoms of mental retardation and learning disabilities seen with septum pellucidum lesions, although its role remains unclear as suggested by the inconsistent correlations of this neuro-anatomic finding with symptoms in schizophrenia.

In a study of Gustavo & al. (2003), they reviewed the MRI findings of 30 patients with non-specific mental retardation. In accordance with the established literature, the study showed a high frequency of brain malformations in mental retardation. The most frequent supratentorial findings were: corpus callosum hypoplasia (43.3%), ventriculomegaly (33.3%), enlargement of subarachnoid spaces (16.6%), cavum vergae or septum pellucidum cysts (33.3%) and cortical dysplasias (23.3%). Moreover, enlarged CSP has been associated with cognitive dysfunction in heterogeneous pediatric groups showing neurologic abnormalities, mental retardation, and developmental delay.

Nopoulos& al. (2000) extend these findings by showing that there is a direct relationship between severity of this anomaly and cognitive function. That is, the larger the anomaly, the greater the cognitive dysfunction. Moreover, the relationship was not specific to any particular type of cognitive skill, but instead was related to global disturbances of cognitive functions: the inverse correlations between size of CSP and cognitive function were significant for full scale, verbal, and nonverbal IQ. This suggests not only that enlarged CSP is a marker for cerebral maldevelopment, but also that the larger the anomaly, the greater the functional deficit, likely reflecting a greater degree of neurodevelopmental aberration.

Renier& al. in their study of Apert's syndrome found that although brain abnormalities such as enlarged ventricles and corpus callosum dysgenesis were often present in these patients, only the septum pellucidum abnormalities were correlated with cognitive dysfunction (lower IQ).

Bodensteiner& al. have repeatedly documented the association with large CSP and a broad range of developmental problems, including mental retardation, developmental delay, seizures, macro/microcephaly, and others. Their work clearly indicates that an enlarged CSP is an important marker for increased risk of disturbed brain development.

In the other hand, as the SP is actively connected to the limbic system, it is known to have an important role in schizophrenia; so, a relevant question is whether the association between midline structural abnormalities and psychotic disorders is directly causal, indirectly contributory, or merely an intriguing epiphenomenon. If midline malformations play a causal or contributory role in psychotic disorders, they might do so via several mechanisms. They might cause failure to modulate normally the activity of limbic and/or cortical structures or regions to which they project, or they might lead to failure in the normal transmission of inputs or outputs carried by the SP to or from cortical or limbic structures. Therefore, a proposed possible mechanism states that, if an anomaly occurs in the SP, disturbances in communication between those systems might occur, resulting in aberrant emotional, cognitive, and behavioral characteristics, similar to the clinical characteristics of schizophrenia. Many studies tend to support the association between midline structural abnormalities and psychotic disorders, including schizophrenia and schizoaffective disease.

Previous studies have demonstrated that schizophrenia is a heterogeneous disorder involving various symptoms manifested by diverse etiologies. Although it might be a small part of the full explanation of the neurodevelopmental mechanisms of schizophrenia.

A large CSP is often considered indirectly related to psychotic disorders and maybe considered a marker for cerebral maldevelopment. A meta-analysis studying CSP in schizophrenia spectrum disorders (SSD) revealed that normal variations in small-sized CSPs were not related to SSD, whereas a large CSP tended to be a risk factor. In recent years, cross-sectional studies have failed to find significant differences in the prevalence of large CSP between psychosis patients and healthy controls. Furthermore, a molecular study reported that a significantly larger CSP was associated with the Disrupted-in-Schizophrenia-1 (DISC1) Ser704Cys polymorphism, although this variant was not found to be unique to schizophrenia patients. Uematsu and Kaiya (1989) reported that CSP was significantly related to family history of schizophrenia.

Thomas F. & al. (1993), to investigate a possible association of midline cerebral malformations with psychotic disorders, MRI and CT scans were blindly evaluated for 52 patients with schizophrenia, 8 of the 52 had abnormalities of the septum pellucidum (SP): 5 had cavum vergae (CaV), 2 had cavum septum pellucidum (CaSP), and 1 had agenesis of the corpus callosum and SP. The results of the study appear to strengthen the association between various types of midline structural abnormalities involving the SP and psychotic disorders, including schizophrenia. Alternatively, as Carey & al. data suggest, anatomical abnormalities of the septal area or other midline structures such as the SP that result in aberrant neuronal function might directly or indirectly produce psychotic symptomatology and behavior. Furthermore, a recent longitudinal study reported that CSP length increased at a higher rate in first episode psychosis patients, which may explain the higher prevalence of CSP in chronic cases, whereas increased CSP length in patients may be caused by the effects of antipsychotics or the duration of illness.

Conclusion:-

Over the past years, multiple cases of patients with Schizophrenia and/or mental retardation revealed, on brain imaging, significant abnormalities in midline brain regions such as Septum Pellucidum. It is suggested that CSP, particularly if large, should be considered a developmental anomaly that may contribute to neuropsychiatric abnormalities. Whether the CSP may serve as a risk factor for psychosis or is only a reflection of neuroanatomical changes in individuals with chronic psychotic disorders remains ambiguous. More studies and case reports will be needed to establish the veritable association of CSP and neuropsychiatric disorders in the future, and perhaps to acknowledge the CSP as an early marker and predictor of psychosis.

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