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Primary Empty Sella Syndrome, Midline Brain Abnormalities and Psychiatric Illness

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Abstract

Primary Empty Sella Syndrome (PESS) is a condition where pituitary gland is partially or completely absent from the sella turcica due to abnormal development of the diaphragma sellae. Although PESS has not been investigated much in relation to psychiatric illness, a few cases have been reported. With review of cases, this article looks into the relationship between PESS and psychiatric illness and possibility of considering PESS as an indicator of midline developmental brain abnormality.

1. Introduction

1.1 Empty sella syndrome

Empty sella turcica is a radiological finding, which is often thought to be an incidental finding and of no clinical significance [1]. In 1951 Busch studied 788 post mortem brains anatomically and introduced the term Empty Sella Syndrome (ESS). About a third of people with radiological finding of empty sella has various degrees of symptoms and develops Empty Sella Syndrome [1-3].

Empty sella turcica may be Primary, develops as result of deficient development of diaphragma sellae, or secondary, which could be due to partial or complete destruction of the pituitary gland from reasons like infarction, haemorrhage, tumor, surgery or radiotherapy [1, 2].

The symptoms of PESS may be as minor as mild headache to chronic lateral headaches, neurological symptoms like dizziness, syncope, cranial nerve related symptoms, seizures; ophthalmic symptoms like blurred vision, double vision, transient visual loss or visual field defects; CSF rhinorrhea, endocrinal symptoms secondary to pituitary hypo function; psychiatric symptoms like depression, anxiety psychosis or schizophrenia spectrum disorders [1-4]. Idiopathic Intracranial Hypertension (IIH) is a rare condition which is found to be associated with ESS in 95% of cases [5-7].

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1.2 Midline brain abnormalities associated with psychiatric illness

Cavum septum pellucidum (CSP) have been found to be associated with neurodevelopmental disorders like schizophrenia, neurophysiological disorders, lower IQ, low verbal memory [8-10].

Dysgenesis or agenesis of septum pellucidum has been found to be associated with schizophrenia [10,11].

Absent adhesio interthalamica (AAI) has been found to be associated with depression [8, 9].

Psychotic and mood disorders are found to be moderate to strongly associated with AAI and CSP of any size [8].

1.2.1 Psychiatric disorders associated with midline abnormalities:

- Schizophrenia spectrum disorders,
- Intellectual developmental disorders.
- Autism
- ADHD.
- Tourette's syndrome.
- Mood Disorders
- FASD

1.3 Beginning of development of midline structures

The human brain is divided into right and left hemispheres with the midline structures in the middle. The midline structures have been an area of interest in recent years and several studies have found association between midline brain abnormalities with psychiatric and neurological symptoms. Brain development begins around the 3rd week of gestation with the development of the undifferentiated neural plate, which later becomes the neural tube [11].

PESS is thought to be due to deficient development of the diaphragma sellae, which is a fold of dura mater (DM) covering the pituitary fossa at the middle of the base of the brain. DM derives from the mesenchymal tissue surrounding the neural tube. Although thought to be inert avascular fibrous tissue, DM is found to be highly vascular. The meninges are also found to be carrying stem cells for brain cell formation in the early life. Development of all these structures appear to start around the same time as the neural tube development [4-6].

In around 3rd week of gestation a protein called sonic hedgehog protein (Shh) is secreted from the cells immediately below the centre of the future neural plate and neural tube, which triggers their formation. Shh protein has been an area of research in terms of brain development and found to be an important factor in development of cranial base in animal model. Shh protein can get mutated due to genetic or environmental factors during pregnancy and post-partum, which can affect the development of midline brain structures [6,7]. Other proteins Bmp7 and WNT proteins have been found to have important role in development of midline structures [19].

1.4 Important factors for Midline brain development

Sonic hedgehog protein (shh) : is an important factor for initiating the signal for formation of neural plate. Shh signalling is important for development of cranial base. Defect in shh protein can cause midline developmental abnormality e.g. holoprosencephaly, midline facial/ pharyngeal abnormalities, neurodevelopmental disorders.

Bone marrow morphogenetic 7 proteins (Bmp): is an responsible to initiate differentiation of the peripheral neuroectoderm to epidermis by sending inhibitory signals to the wnt proteins.

WNT proteins: responsible for initiating induction and patterning of the nervous system. It sends inhibitory signals to BMP proteins in the region of neural plate so that those cells remain undifferentiated and become neural plate.

Considering the importance of the role of these factors in midline brain development and importance of these structures, for proper brain functioning and information processing this article tries to present a few cases with psychiatric and neurodevelopmental symptoms and their radiological findings .

2. Case Presentations

2.1 Case 1

24 year old single man with ESS, admitted to adult psychiatry unit. Presented with visual hallucinations of images of giant spiders and distorted human figures; tactile hallucination of something crawling on his skin and associated tingling and feeling of numbness in one side of his body. Comorbid symptoms of visual difficulties, distorted images with increasing sensitivity to bright light and sound. These symptoms were present for about a year, worsened for about 2 months prior coming to the hospital.

No History of alcohol, drugs or nicotine.

Past psychiatric history: At age 8, diagnosis of borderline learning disability and completed high school with below average grades. At the age of 11, he was diagnosed with oppositional defiant disorder (ODD) and attention deficit hyperactivity disorder (ADHD). He was not on any medication and did not have any psychiatric follow up for years after that, until his recent presentation with psychotic symptoms.

He was diagnosed with congenital valvular heart disease, waiting for surgical repair of his heart valves.

Family history was positive for, mother - fibromyalgia, maternal grandmother-Schizophrenia and great grandfather - bipolar disorder. His paternal grandfather was diagnosed with multiple sclerosis.

He struggled in school and was unable to keep a steady job. He preferred to stay by himself as he felt socially awkward.

He underwent ophthalmological examination that ruled out major ocular problems and was diagnosed with possible ocular migraine.Neurological examination excluded major neurological disorders, but neurological aetiology of visual hallucinations could not be ruled out.

He was investigated for pituitary hormones but no major abnormalities were noted.

2.2 Investigations

Blood work: Mostly normal except low free testosterone and slightly low luteinizing hormone.

CT scan of the head: Showed a small region of white matter low density in the right frontal lobe. The sella turcica appeared nearly empty.

MRI head with/ without contrast: Showed increased FLAIR/ T2 signal near anterior horn of right lateral ventricle (upto.1.2 cm), small pericallosal & periventricular lesions as well as few subcortical lesions, mostly in anterior region and sparing occipital lobes. No mass effect was evident.

EEG: Showed dysrhythmia with occasional slowing in right temporal region. High amplitude sharp slow complexes were prominent in frontal region. The EEG was interpreted by a neurologist as nonspecific and not suggestive of epilepsy.

Echocardiogram: Showed bicuspid aortic valves with mild aortic stenosis and mild aortic regurgitation.

Psychological tests: Had Full-Scale IQ in the average range of intellectual functioning (42nd percentile) on the Wechsler Abbreviated Scale of Intelligence (WASI-II). His Executive function indicated mildly impaired task planning and moderately impaired verbal working memory. His Perceptual-motor skills did not show deficits in visual or motor functions.

Diagnosis: Unspecified psychosis.

Differential diagnosis: Psychosis secondary to other medical condition, Schizophrenia spectrum disorders.
Treatment: Inpatient Management, relevant investigations and treatment with antipsychotic medication Olanzapine.

2.3 Case 2

A 36 year old Indigenous female with 8 children presented with -Severe postpartum psychosis with catatonic features: mutism, catalepsy with blank staring, auditory & visual hallucinations, delusions of killing her children.

Past psychiatric history**:** Postpartum depression and postpartum psychosis during previous pregnancies, Intellectual disability disorder & FASD.

Past medical history: Hypothyroidism.

2.4 Investigations

CT brain scan: reported "partially empty sella, generally of no clinical significance" and "calcification of pineal gland , generally a common finding and of no clinical significance"

MRI brain: flattened pituitary gland.

Blood work: showed low thyroid hormones.

Psychological tests: low scores, consistent with previous diagnosis of intellectual disability.

Diagnosis: Postpartum psychosis, IDD, FASD, hypothyroidism.

Management: Inpatient management, antipsychotic medication – paliperidone to treat acute psychosis, antidepressant medication fluoxetine to treat comorbid depression + treatment of associated disorders. Response to treatment was very slow due to the severity of symptoms.

2.5 Case 3

An 18 year old male with previous diagnosis of ADHD &? Asperger's syndrome as a child was brought for psychiatric assessment by his father due to severe social anxiety. He was refusing to go out of his house, unless it is absolutely necessary, spending time alone mostly playing video games or sleeping. He also had repetitive behaviours like checking self-doubt, obsessions of germs and compulsions of checking, hand washing. He lacked motivation, struggled with planning organizing as well as lacked social skills. He had no friends.

Past Psychiatric History: Remote history of seeing a psychologist who diagnosed him with ADHD and possible Asperger's syndrome when he was about 12 years old.

Medical history: Was positive only for mild hypothyroidism, for which he was not on any treatment.

2.6 Investigations

Blood work: Elevated TSH levels with borderline low thyroid hormones.

CT head: Reported empty sella that stated "no significant intracranial abnormality"

MRI: Could not be performed at the time due to patient's anxiety.

Diagnosis: unspecified neurodevelopmental disorder, social anxiety disorder, OCD.

Management: started with fluoxetine for social anxiety and OCD which improved his symptoms significantly. Then he was started on lisdexamfetamine to improve his executive dysfunction, which made significant improvement.

3. Discussion

PESS is often considered an incidental and unimportant finding and has not got much attention by clinicians. But as we are starting to know more about developmental biology of psychiatric disorders, we are finding more and more evidence that findings like ESS may actually indicate some possible underlying developmental deficits. All of the above three cases showed incidental finding of empty sella turcica during routine CT head scans. Could it be a part of overall neurodevelopmental picture is an important question. With this question in mind, we can also explore the possibility to consider primary empty sella as an indicator of midline developmental brain abnormality.

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