

SHORT REPORT

Schizencephaly associated with psychosis

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Abstract

Schizencephaly is a rare disorder of brain development resulting in the formation of abnormal unilateral or bilateral clefts in the cerebral hemispheres. It is often accompanied by partial seizures, mental retardation, and hemiparesis. Two patients are described with clear psychotic symptoms with either unilateral or bilateral schizencephaly. The implications of the association between schizencephaly and psychosis in these patients for understanding the biology of the psychoses are discussed.

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Originally described by Wilmarth¹ and later by Yakolev and Wadsworth,^{2,3} the schizencephalies are rare abnormal unilateral or bilateral clefts in the cerebral mantle arising during early prenatal development. The clefts most commonly involve the parasyllvian regions and have been divided into two subtypes. Type 1 schizencephalies are clefts with fused lips,² whereas type 2 schizencephalies have separated lips and accompanying hydrocephalus.³ Schizencephaly usually presents in childhood with seizures, motor dysfunction, and intellectual impairment.⁴⁻⁷ The degree of intellectual and motor dysfunction seems to be related to the amount of brain involved.⁵

Psychotic symptoms have been reported in association with a wide array of brain abnormalities or injuries,^{8,9} but there have been no previous reports of psychotic symptoms in patients with schizencephaly. We describe below two patients with schizencephaly who had a psychotic disorder.

Case reports**PATIENT 1**

This woman had had several admissions to psychiatric hospitals for either psychotic episodes or depressive states accompanied by suicide attempts. She was born with left sided weakness, reduced vision, and strabismus in her left eye. She had delayed developmental milestones, received the diagnosis of cerebral palsy at the age of 2, and was subsequently

found to be mentally retarded. Seizures started at the age of 7 and she was treated with carbamazepine with good effect.

She had her first admission to psychiatric hospital at the age of 18 after she began to hear voices, which were accompanied by religious preoccupation and grandiosity. She was given the diagnosis of schizophreniform disorder and treated with neuroleptic drugs. Her symptoms improved but her social functioning remained impaired. Over the next nine years the patient was admitted to hospital eight times at different institutions. The admissions were mainly for depressive symptoms, suicidal ideation, social withdrawal, and abnormalities of thought processes. She was treated at different times with therapeutic doses of haloperidol, loxapine, fluphenazine, perphenazine, nortriptyline, sertraline, and benzotropine either singly or in combination. Her symptoms were usually temporarily alleviated but not eliminated during psychiatric admissions.

During her most recent admission, she displayed depressed mood, feelings of hopelessness, sleep and appetite disturbances, religious and persecutory delusions, and auditory hallucinations. On physical examination she had dysarthria, left sided strabismus, brisk reflexes in her left limbs, and gait disturbances consistent with cerebral palsy. The results of all blood tests, chest radiography, and ECG were within normal limits.

The Wechsler adult intelligence scale—revised (WAIS-R) gave scores in the mentally retarded range, with a full IQ score of 63, a performance IQ score of 60, and a verbal IQ score of 67. She was also impaired on the wide range achievement test—revised (WRAS-R) and Bender gestalt visual-motor test with difficulties in arithmetic and timed tasks.

Brain MRI disclosed bilateral schizencephaly of the closed lip (type 1) variety with clefts in the frontal lobes extending from the lateral frontal cortex deep into the white matter to the level of the ventricles (fig 1). The clefts were superficially surrounded by grey matter. There was also irregular thickened grey matter aligning the lateral ventricular walls consistent with grey matter heterotopias. The septum pellucidum was absent, consistent with septo-optic dysplasia. The corpus callosum was normal and fully developed. The pituitary, parasellar, and pineal regions were unremark-

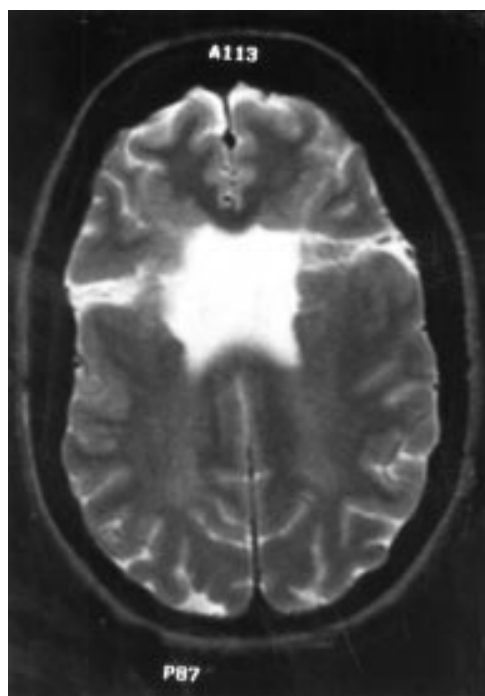


Figure 1 MRI of patient 1. The T2 weighted image shows bilateral CSF clefts and absence of the septum pellucidum.

able. There was no evidence of infarction. Brain MR angiography was essentially normal, with the exception of a fetal origin of the left posterior cerebral artery.

The patient was treated with trifluoperazine, trazodone, and carbamazepine. She showed some improvement in her depressive symptoms but remained psychotic at the time of discharge.

PATIENT 2

Patient 2 was a 29 year old man with a history of psychotic symptoms. He was born with right sided monoplegia, thought to be secondary to cerebral palsy, and had perinatal hyperbilirubinaemia. Learning problems became evident at the age of 8. He was seen by the school psychologist at the age of 14 for acting out and poor self care, and was thought to have an adjustment reaction of adolescence with conduct disturbance and depressive traits. Intelligence testing showed a normal IQ. His family psychiatric history was notable for a paternal half uncle who had undifferentiated schizophrenia.

The patient was first admitted to hospital at the age of 16, after he developed social withdrawal, persecutory delusions, and auditory hallucinations. He displayed an inappropriate affect and was given the diagnosis of undifferentiated schizophrenia. He was treated with haloperidol and procyclidine but was poorly compliant with his medication. At the age of 19 he was taken off medication and his mental status deteriorated; he did poorly and was eventually transferred to a psychiatric hospital. On admission, he was grossly psychotic and reported auditory hallucinations, ideas of reference, thought insertion and withdrawal, persecutory delusions, and suicidal ideation. His hygiene was poor, his affect was blunted,

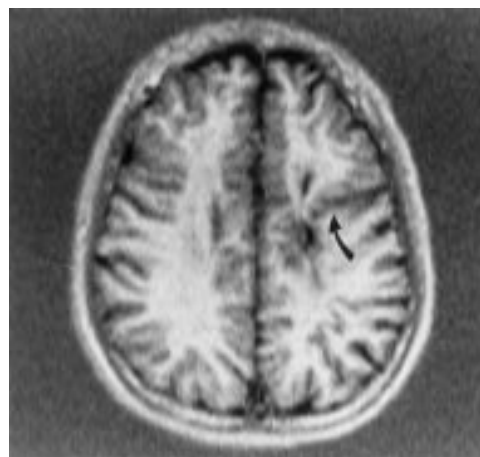


Figure 2 MRI of patient 2. The image was obtained with an inversion recovery sequence and shows a left sided, unilateral frontal cleft (arrow).

and appetite, concentration, and sleep were diminished.

Brain CT and MRI were performed. The CT was initially read as normal by a general radiologist; however review with a neuroradiologist indicated a deep, left frontoparietal sulcus. The inversion recovery sequence of an MRI study showed a left sided unilateral schizencephalic cleft, lined with grey matter and with loss of the adjacent white matter (fig 2). A proton density sequence showed an area of increased signal over the cleft, consistent with reduced myelination of nearby white matter.

Patient 2 was unresponsive to haloperidol, lithium, and carbamazepine, and deteriorated when given brief trials of nortriptyline and clomipramine. He underwent a course of nine electroconvulsive treatments (ECT) augmented with carbamazepine and pimozide. His mood improved significantly after ECT, but he remained psychotic. Since his discharge from hospital, he has been complying with his treatment as prescribed by a community psychiatrist. He is currently treated with risperidone. At times, he has prominent depressive symptoms, and has had intermittent antidepressant treatment. He remains psychotic during his depression free intervals.

Discussion

Schizencephaly is one of a group of malformations, including pachygyria, polymicrogyria, and heterotopia, which are the result of abnormal brain development during the first six months of gestation.¹⁰ Some lesions classified as schizencephaly may be due to encephaloclastic lesions from intrauterine cerebral infarction leading to porencephaly.¹¹⁻¹³ Yakolov and Wadsworth² have argued persuasively that "true schizencephaly can be distinguished from porencephaly by its unique neuropathology and associated abnormalities". They further hypothesised that schizencephaly is the result of abnormal neuronal migration occurring during the first half of the first trimester. Others have argued that the presence of polymicrogyria lining the clefts in schizencephaly indicates that these abnormalities are formed in the early part of the second trimester.⁵ Whether

schizencephaly represents a primary disorder of neuronal migration or is the consequence of an insult followed by secondary disruption of neuronal migration is unknown. The recent identification of mutations in the homeobox gene *EMX2* in three patients with type 2 schizencephaly suggests that genetic factors may be operative in some patients.¹⁴

A key question is the importance of the association between schizencephaly and psychosis in the two cases presented. The two patients show some interesting similarities. Both experienced auditory hallucinations, delusions, and prominent depressive symptoms and could be given the DSM-IV diagnosis of schizoaffective disorder. Also, both patients experienced a relatively early onset of psychosis and have had a poor response to treatment. The similarity in phenomenology lends support to the hypothesis that schizencephaly is related in some way to the development of psychosis in these patients. A definitive statement that the psychosis in each patient is due to schizencephaly, however, can obviously not be made. Given the history of seizures which preceded the psychosis in patient 1, an alternative diagnosis in her case is psychotic disorder due to epilepsy.¹⁵ History of schizophrenia in the family (albeit distant) of patient 2 could have more to do with his psychosis than his schizencephaly. There are also some important differences in their clinical pictures. Patient 1 has left sided motor impairment, whereas patient 2 has a right sided monoplegia. Consistent with her more extensive bilateral lesion, patient 1 has significant cognitive impairment and seizures, whereas patient 2 has a learning disorder but a normal IQ.

If schizencephaly is related to the development of psychosis in these patients, a possible mechanism is the disruption in intracortical connections.¹⁶ Deficits in mechanisms of focal activation of cortical activity (hypofocality) has been hypothesised to be general features of the schizophrenic cortex.¹⁷ The theory that schizophrenia is associated with abnormal brain development has gained widespread acceptance.^{17, 18} Specific neurodevelopmental abnormalities, including midline cerebral malformations of the septum pellucidum and corpus callosum, have also been postulated to be

related to schizophrenia.¹⁹ Convincing evidence of a neurodevelopmental origin to schizophrenia, however, remains elusive. The possible association between psychosis and schizencephaly in the two patients presented may provide an example of a neurodevelopmental abnormality that manifests as psychosis after a long delay.

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