Midline brain anomalies and schizophrenia in people with CATCH 22 syndrome

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Background Since people with chromosome 22q11 deletion (CATCH 22 syndrome) have unexpectedly high incidence of major psychosis it has been suggested that 22q area might be involved in the pathogenesis of schizophrenia and bipolar disorders.

Method A single case report.

Results A 32-year-old male patient with CATCH 22 syndrome and schizophrenia had extensive midline anomalies of the brain in the regions relevant to psychotic disorders.

Conclusions 22q11-dependent abnormalities in the midline structures of the brain may cause dysfunction in the limbic system and interfere with the interhemispheric information exchange thus predisposing people with CATCH 22 syndrome to psychotic disorders.

CASE REPORT

The subject was a 32-year-old male with congenital palatal cleft and asymptomatic ventricular septal defect. He had no family history of psychiatric or developmental disorders. He went to a normal elementary school until the age of 12, when he had to be transferred to a special class because of learning difficulties. Four years later he developed paranoid psychotic symptoms claiming that 'the Finns' were trying to kill his family and take away all the precious things in his life. These threatening plans were transmitted to him by voices from televisions, which he started to fear and avoid. He had a grandiose delusion of being a gifted guitar-player of international class. Eventually, at the age of 20 he became so aggressive towards his father that he had to be admitted to an institution, where paranoid schizophrenia was diagnosed. The disease ran a chronic course with severe psychotic symptoms, aggressiveness and suicidal tendencies which could only slightly be blunted with large doses of sedative neuroleptics. Clozapine, at a dose of 800 mg/day had a dramatic effect on his psychotic symptoms. His suicidality and hostility disappeared while the auditory hallucinations have remained chronic. After the introduction of clozapine, he developed occasional grand mal-type convulsions. Since the reduction of clozapine dose caused rapid deterioration of the psychotic symptoms, oxcarbazepine medication was introduced to control the convulsions with good results. The electroencephalogram showed markedly increased delta- and theta-wave activity with spikes and slow-wave paroxysms, a typical finding in people receiving clozapine medication. The subject did not suffer any manic or depressive episodes. After a long rehabilitation process the subject was able to live in a sheltered residential home for people with learning disabilities.

Throughout clinical examination the subject was oriented and cooperative, but gave a childish and retarded impression. He had a high, nasal slurred voice because of cleft palate. His nose was broad, his eyes were slightly hypertelorism and he had a bilateral internuclear ophthalmoplegy without diplopia. This disturbance of conjugate eye movement is usually caused by abnormality of the medial longitudinal fasciculi of the brain stem at the midline. In our subject, the aetiology of this feature was probably developmental. His fingers were short and the distal phalanxes were dysmorphic. In psychological testing he had visuo-spatial and visuo-constructive...
defects along with low intelligence quotient of 63.

Magnetic resonance imaging at 1.0 T revealed a large cavum septum pellucidum (CSP; see Fig. 1) and a hypoplastic vermis of the brain. No anomalies of brain stem or corpus callosum were visible. The presence of 22q11 microdeletion was verified with fluorescent in situ hybridisation with a DNA probe specific to 22q11 region (D22S75).

DISCUSSION

Midline brain anomalies and schizophrenia

Many investigators have shown that the most common midline anomalies of the brain, such as CSP, have increased incidence in people with schizophrenia (Lewis & Mezey, 1985). Contrary to the previous belief of septum pellucidum as a neurologically mute membrane, its importance as a relay station of the limbic system linked with hippocampus and hypothalamus as well as corpus callosum has been recognised, possibly explaining its association with schizophrenia and other neuropsychiatric disorders (Sarwar, 1989). Other chromosomal anomalies such as partial trisomy of chromosome 5 have also been linked to CSP and schizophrenia (Honér et al, 1992). The role of cerebellum in cognitive and behavioural processes has only quite recently been understood, and hypoplastic vermis, another midline anomaly in our subject has been associated with schizophrenia (Martin & Albers, 1995).

Midline brain anomalies in people with CATCH 22 syndrome

Little is known about the brain anomalies in people with CATCH 22 syndrome. Papulos et al (1996) stated in their article regarding bipolar psychiatric disorders in these subjects that:

"none of the 12 patients who received MRIs had cortical lesions or anomalies of the putamen, caudate or corpus callosum, although a small vermis, as well as cysts adjacent to the frontal horns, was not an uncommon finding."

Mitnick et al (1994) reported a series of 11 (mostly paediatric) subjects, nine of whom had brain anomalies, mostly small vermis, small posterior fossa and small cysts by the anterior horns.

Possible mechanisms behind midline brain anomalies and psychiatric disorders

During the embryogenesis, the development of midline structures like the heart, thymus, palatine and midline of the brain are parts of a single developmental field. The formation of these structures during the early weeks of the embryogenesis are regulated by the formation, migration and action of cephalic neural crest cells. Many factors, such as toxic (maternal alcohol consumption or retinoids), metabolic (maternal diabetes mellitus) or chromosomal (trisomy 5, 10p deletion or 22q deletion) can disturb the normal succession of these events, which may lead to midline malformations of the developing fetus (Lammer & Opitz, 1986).

Our subject had typical CATCH 22 features with midline craniofacial abnormalities and ventricular septal defect. More interestingly, he had also multiple structural and functional midline malformations of the brain suggesting an extensive developmental disturbance of his nervous system.

We suggest that the 22q11 deletion in our subject caused not just the cleft palate and ventricular septal defect as a part of the CATCH 22 syndrome, but midline brain in his septum pellucidum, cerebellum and brain stem as well. The maldevelopment of the midline brain structures and intercrossing projections cause disturbances in the interhemispheric communication and may explain not just the psychotic symptoms in our own subject, but the high incidence of major psychiatric disorders in other people with CATCH 22 syndrome as well. Thus, the midline disorganisation of the brain may be one of many optional pathways leading to the syndromes of schizophrenia or bipolar disease.

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REFERENCES


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