Interictal Schizophrenia-like Psychosis in a Patient With Double Cortex Syndrome

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The authors report a female patient with sporadic double cortex syndrome who manifested recurrent interictal schizophrenia-like psychoses. She had no mutations in the doublecortin *gene but a pericentric inversion of chromosome 9. Neurodevelopmental disturbances and seizures may be associated with her mental dysfunction.*

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Double cortex syndrome (DC; also known as subcortical laminar heterotopia) is a generalized neural migration disorder that is characterized clinically by intractable epilepsy and mental deficiency.[1] In DC, a subpopulation of neurons appears to be arrested in the subcortical white matter and forms a second layer of gray matter.[1] All familial DC and approximately one-third of sporadic DC cases have mutations of the *doublecortin* (*DCX*) gene in Xq22.3–q23.[2,3]

Abnormal neural migration patterns have recently been reported in patients with schizophrenia.[4] Cytogenetic abnormalities related to schizophrenia have also been reported.[5,6] It is of interest if patients with distinct cell migration abnormalities or cytogenetic alterations exhibit schizophrenia-like symptoms.

Here we report a female patient with sporadic DC who developed schizophrenia-like psychosis.

CASE REPORT

History of epilepsy and psychosis. The patient is a right-handed 39-year-old Japanese woman. Her family members (parents and two brothers) had normal cognitive functions and no neuropsychiatric disorders and have adapted themselves to the community well. She entered an ordinary elementary school, although her early developmental milestones were somewhat delayed.

At age 10, she developed complex partial seizures (CPS), characterized by aura, loss of consciousness with eye deviation to the left, occasional brief tonic movement of both arms, and subsequent generalized tonic-clonic seizures (GTC). She suffered epileptic seizures 3 to 4 times per month. Since her first seizure, she has shown a progressive mental decline, which necessitated her transfer to a special class at age 12. Since graduating from a special high school for mentally handicapped persons, she has commuted to a workshop for the disabled.

At age 25, she developed delusions of persecution and reference without any preceding explanatory psychosocial events. She had visual hallucinations of ghosts and monsters and probable auditory hallucinations. She exhibited some unusual mannerisms (walking around talking to herself and staring extendedly at photos of a popular singer) and obsessive behaviors (flushing the toilet every 15 minutes). During these episodes, her consciousness was clear and her orientation was intact. Administration of an antipsychotic drug (levomepromazine, 150 mg per day) improved her mental state within 2 months. She had three more psychotic episodes with similar symptoms, and levomepromazine was found to be effective again. Since her first psychosis occurred, the frequency of seizures has decreased to 1 to 2 times per year for the past 15 years. Her personality has not altered throughout her clinical course except during psychotic episodes. She has taken 600 mg of carbamazepine per day (serum level; 9.7 μg/ml).

Investigations. EEG showed well-developed 9-Hz to 11-Hz occipital rhythms and bilateral epileptiform discharges with predominance over the left frontotemporal region. During the four psychotic episodes, EEG has not normalized. Brain MRI revealed bilateral bands of heterotopic gray matter in the centrum semiovale, separated from cortical gray matter by layers of white matter (Figure 1). Diffuse atrophy of the cerebral hemispheres was also observed, although the gyral and convolutional patterns of the overlying cortex were normal. The limbic structures were unremarkable. Interictal brain SPECT images with [^{99m}Tc]HMPAO have been reported elsewhere.[7] Briefly, they revealed identical or increased perfusion of the subcortical laminar heterotopia, compared with that of the overlying cortex, and hypoperfusion of the left temporal lobe.

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Neurological examinations were unremarkable. Tanaka-Binet IQ Scale score was 38 at age 35 years.

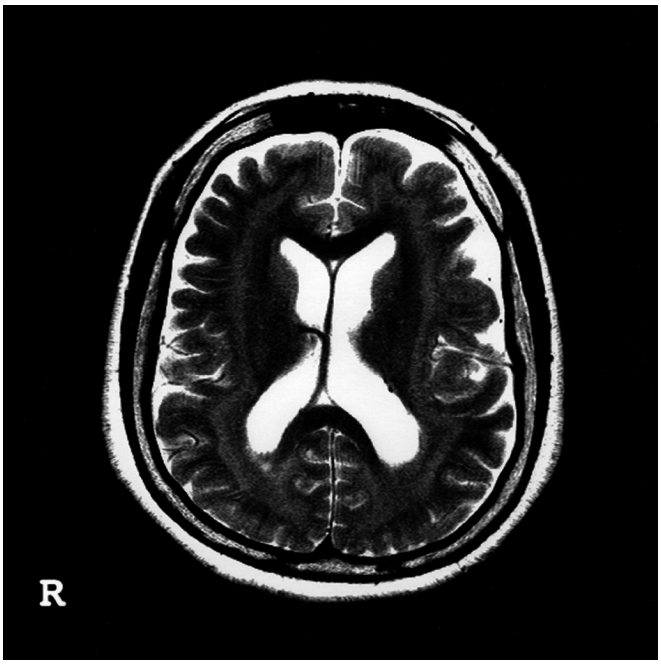
Chromosome aberration. The patient and her mother underwent chromosomal and genetic studies after giving written informed consent. Cytogenetic examination using GTG banding revealed that the patient had a pericentric inversion of chromosome 9, a karyotype of 46XXinv(9)(p12q13). Her mother also had this chromosomal abnormality.

Mutation analysis. Genomic DNA was extracted from white blood cells. To scan regions of *DCX* covering the branch site of each intron and the 5′-upstream sequences of exon 1A, we determined the following sequences by using Genome-Walker Kits (Clontech, Palo Alto, CA, USA): 325 bp upstream of exon 1A and 146 bp of intron 1B 3′-portion (DDBJ/EMBL/GenBank Accession Nos.: AJ005591–AJ005597). Polymerase chain reactions (PCRs) were performed by using a Gene Amp 9700 thermal cycler (PE Applied Biosystems, Chiba, Japan) under the conditions shown in Table 1. PCR products were sequenced directly in both directions with a BigDye terminator kit and an ABI 377 DNA sequencer (PE Applied Biosystems). Mutations in the gene *DCX* were not detected in this patient or her mother.

DISCUSSION

This patient's clinical characteristics and brain MRI findings were consistent with double cortex syndrome.

FIGURE 1. Axial T_2-weighted MRI image at age 38. The symmetrical bands of heterotopic gray matter are present in both hemispheres from the frontal to the occipital region. Moderately enlarged ventricles and cortical sulci are remarkable.



She developed interictal schizophrenia-like psychosis without any explanatory preceding psychosocial events.

As for an underlying genetic abnormality of this patient, we failed to detect any alterations in the *DCX* gene, including all possible branch point sequences in the 3′ portions of introns. To our knowledge, this is the first report to analyze extended intronic regions, including potential branch sites, to examine possible splicing-related abnormalities. In sporadic DC patients, mutations in the coding regions of *DCX* mutation are less frequently identified than in familial DC patients. Recent investigation[3] suggested that genetic heterogeneity may exist for DC and may be explained by other types of mutations of *DCX* outside the regions already examined, or by mutations of other genes. In addition to further studies on genetic and structural aspects, functional neuroimagings may facilitate disclosure of the relationship between the diversity of DC and its symptoms.[8]

This patient had a pericentric inversion of chromosome 9 [inv(9)], probably transmitted maternally. Although inv(9) has been observed in persons without any specific phenotypes such as her mother, schizophrenic patients have this inversion more frequently than do individuals in the general population.[5] Recent studies on schizophrenia revealed that the pericentric region of chromosome 9 might be associated with its pathogenesis.[5,6] It is possible that the inv(9) in our patient might be associated with some vulnerability to a schizophrenia-like psychosis.

Many patients with schizophrenia have been reported to have cytoarchitectural abnormalities in brain tissues that are assumed to result from abnormal neuronal development.[4] Some cytoarchitectural disturbances in our patient may be extreme compared with those seen in schizophrenic patients and may cause the serious mental dysfunction through modifications of neural pathways that resemble those of schizophrenics.

Psychiatric features of DC patients have not been well documented, except for behavioral problems such as impulsiveness, aggression, and unstable emotions. Patients with DC commonly suffer from varying degrees of mental retardation.[1] This patient has showed mental decline since the first seizure occurred. Mental deterioration due to recurrent seizures has not been often observed.[9] Meanwhile, in some DC patients reported,[10] uncontrolled seizures together with underlying neural migration disorder appeared to result in mental decline.

People with mental retardation, especially when it is complicated by organic brain disorders, are liable to develop psychotic features.[11] These psychiatric vulnerabilities are often related to a reduced capacity to cope with complex social and cognitive demands and to difficulty in solving problems.[11,12] However, this patient's epi-

sodes were not simply derived from her mental disturbance, since similar psychotic symptoms occurred four times without any specific psychosocial stressors and lasted for several months each time.

Patients with epilepsy have an increased risk of developing interictal schizophrenia-like psychosis.[13,14] The patient's epilepsy type (focal epilepsy) and seizure types (CPS and GTC) corresponded to the risk variables.[14] However, the seizure frequency and the antiepileptic drugs administered were unremarkable around the periods of her psychotic episodes. Despite the lack of a distinct relationship between the surface EEG findings and psychotic episodes, frequent EEG discharges in the frontotemporal regions might be associated with her psychiatric symptoms. It is possible that discharges from diffuse subcortical ectopic tissues propagate irregularly. Some studies have shown that epileptiform discharges in the depth, which are not necessarily recorded in the surface EEG, possibly provoke behavioral changes including psychotic symptoms.[15] Although this patient manifested prominent positive psychotic symptoms, some of her psychiatric features, such as visual hallucination and no personality change, are more consistent with those of interictal psychosis than schizophrenia.[13]

The co-occurrence of the abnormalities in the neural network and the cytogenetic alteration, in addition to epilepsy, may have contributed to this patient's susceptibility to schizophrenia-like psychosis. Further investigation is necessary to elucidate the mechanisms underlying the psychiatric features of patients with DC.

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TABLE 1. Primer sequences and conditions for PCR amplification

Fragment	Primer	Primer Sequence	Size (bp)
5′ upstream	up-F up-R	5′-AGG TTT TGG CCA AGT GAA ATT GC-3′ 5′-CTC ACC GGT TTT CTG CTG GTT G-3′	307
Exon 1AB	1AB-F 1AB-R	5′-GGA ATT TCT TGC TTG GAG CTC AG-3′ 5′-CAT CAC AGT GAA AAC AAA GG-3′	291
Exon 1C	1C-F 1C-R	5′-CCA TTA AGA GGT GTT GCT GC-3′ 5′-GGT TAG CAT CTC CAG CTT AGG-3′	394
Exon 1C-2	1C-F2 1C-R2	5′-TTT TAT GAA TGT CGG ATA GCT GC-3′ 5′-CAG AGG AGA AGG GGA GAT TTT G-3′	435
Exon 2	2-F 2-R	5′-TTG TTT TTG CCT CTC TTC ACC C-3′ 5′-ATG ATG CCA CCT CCC ACC AAC-3′	477
Exon 3	3-F 3-R	5′-GTT CTA CTC CAG TGT CAG TGT G-3′ 5′-GGA AAA GTA CTT TGA AAA AGT ACC-3′	462
Exon 4	4-F 4-R	5′-TGA GGT TCA TTG TCA CAG GAC C-3′ 5′-GAA GGG GAG AGA ACA ATG GAG C- 3′	207
Exon 5	5-F 5-R	5′-GGC TGA TAA CAT GCT GAG CCT G-3′ 5′-GAA GTC AGC GTG CAC AGT TAG G-3′	236
Exon 6	6-F 6-R	5′-GAG GGG AAG GAT AAC TTG CTC C-3′ 5′-GCC ATT CAG GAA ACT GAG TGC A-3′	222
Exon 7	7-F 7-R	5′-AGC AGA CAT TCC AGA GCT CAA G-3′ 5′-CTA GCA CAT TTT GCA TCC CTG G-3′	389

Note: Polymerase chain reactions (PCRs) were performed with DNA polymerase ExTaq (Takara Shuzo, Shiga, Japan) for 5′-upstream, exons 1C, 1C-2, and 3, or with Expand polymerase mixture (Boehringer Mannheim, Mannheim, Germany) for the rest of exons at final concentrations of 0.2 mM dNTPs and 2 (for ExTaq) or 2.25 (for Expand) mM magnesium chloride. PCR cycling conditions were as follows: initial denaturation at 94° C for 5 min followed by 30 cycles of 94° C for 30 s, annealing at 58° C for 30 s, and 72° C (for ExTaq) or 68° C (for Expand) for 60 s, with a final extension for 7 min at 72° C. Annealing temperatures for touchdown PCR for exons 5 and 7 were 10 cycles at 67–58° C and 20 cycles at 57° C.

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