Letter to the Editor

Are Advanced Paternal Age and Point Mutation at Chromosome 4 Associated With Schizophrenia?

To the Editor: Schizophrenia genes are associated with different chromosomal locations in affected family members, but individual genes have not been recognized. Advanced paternal age has now been considered an independent risk factor for developing schizophrenia in adult offspring.[1–3] Schizophrenia is rarely known to co-occur with genetic syndromes of which short stature is also a part.[4–6] Like schizophrenia, achondroplasia is also known to occur as a result of sporadic mutation consequent to advanced paternal age.[7] Here we describe a case of a combination of schizophrenia and achondroplasia associated with advanced paternal age.

Case report. Ms A, a 41-year-old woman with a personal history of dwarfism since birth as well as family history of dwarfism and schizophrenia in her father, who was 44 years old at the time of her birth (her father died 7 years before this presentation due to an accident), presented in 2007 with a 5-year illness, characterized by auditory hallucinations that commented on her actions and gave her commands, delusion of persecution, somatic passivity, and impaired biologic, social, and occupational functioning. Physical examination revealed dextrocardia as well as the classical phenotype of achondroplasia: short stature, rhizomelic shortening of the arms and legs, a disproportionately long trunk, trident hands, midfacial hypoplasia, and prominent forehead.

We made a diagnosis of paranoid schizophrenia (*DSM-IV* criteria) and strongly considered the possibility of achondroplasia. The patient was treated with risperidone (3 mg oral tablets twice per day), and, by the fourth week, the psychotic symptoms had disappeared completely.

Since prevalence of schizophrenia in velo-cardio-facial syndrome is about 24%,[6] we performed fluorescent in situ hybridization, results of which were negative for deletion of 22q11. Her chromosomal analysis showed 46 XX, which ruled out Turner's syndrome.

To the best of our knowledge, this is the first reported case of achondroplasia and schizophrenia occurring in the same individual. Achondroplasia is the most common type of short-limbed dwarfism, and 80%–90% of cases are caused by de novo mutations in the gene for fibroblast growth factor receptor 3 (*FGFR3*) on chromosome 4 (4p16.3).[8] Molecular analysis is required for confirmatory diagnosis, but, unfortunately, financial limitations restricted our intentions.

Achondroplasia and schizophrenia are genetic conditions known to occur as a result of mutations consequent to advanced paternal age. Considering our patient inherited the mutant gene through an autosomal dominant mechanism, such a mutation may have less likely influenced development of both of these disorders as a coincidence in our patient, despite the fact that the age of her father was 44 years at the time of her birth. Here, a sporadic mutation in a "hot spot" in the *FGFR3* gene was responsible for the achondroplasia phenotype in our patient's father. We propose that a single de novo sporadic gene mutation was possibly responsible for both phenotypes and transmitted together to the offspring as autosomal dominant disorders. However, schizophrenia has multifactorial etiology, and environmental factors could have influenced the genetic risk in the pathogenesis of schizophrenia. Many scientists are searching the etiology of schizophrenia, but we have not found the definite answer yet. Our case report is a small trial to discern its etiology.

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