Case Report

Rubinstein–Taybi Syndrome with Psychosis

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ABSTRACT

Rubinstein–Taybi syndrome (RTS) is a rare genetic disorder with characteristic physical anomalies. It is characterized by mental retardation, postnatal growth deficiency, microcephaly, specific facial characteristics, broad thumbs, and big toes. Behavioral problems are common with RTS; they include mental retardation, impulsivity, distractibility, instability of mood, stereotypes, poor coordination, atypical depression, and mania. To date, there is lack of literature on the presence of schizophrenia or non-affective psychosis with RTS. Here, we describe two cases where there is co-morbid psychosis with RTS. One case is diagnosed as paranoid schizophrenia and the other as psychosis possibly schizophrenia. Genetic analysis was not done due to unavailability. The possible etiological factors for the association of psychosis with RTS are discussed. Factors such as regulators of RNA polymerase II and hypoxia-inducible factor 1 alpha (HIF1A) may be some common etiological factors for the association of schizophrenia or non-affective psychosis and RTS. Schizophrenia / non-affective psychosis can be a comorbid psychiatric condition with RTS.

Key words: *Psychosis, Rubinstein–Taybi syndrome, schizophrenia*

INTRODUCTION

Rubinstein–Taybi syndrome (RTS) is characterized by mental retardation, postnatal growth deficiency, microcephaly, specific facial characteristics, broad thumbs, and big toes.[1] The incidence is 1 : 100 000 to 125 000, at birth. It generally occurs as sporadic cases. A cytogenetic or molecular abnormality can be detected in 55% of the RTS patients.[2] A majority of patients have mutations in the gene that encodes the transcriptional coactivator, Cyclic AMP-responsive element-binding (CREB) protein on chromosome 16p13, and about 3% of the patients have mutations in the E1A binding protein p300 (EP300) gene on chromosome 22q13.[3]

The behavioral aspects include a variable degree of mental retardation, impulsivity, distractibility, instability of mood, atypical depression, stereotypes, poor coordination, and overweight.[4,5] There is one case report on recurrent manic episodes associated with RTS[6] and no reports on the association of RTS with schizophrenia or non-affective psychosis.

Here we report two cases who presented with psychosis with RTS. The psychopathology and possible association between both are discussed.

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CASE REPORTS

Case 1

A 31-year-old, unmarried male presented with worsening behavioral problems for two months. He was the first of the three siblings, born of a second-degree consanguineous marriage among parents. He

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had a global developmental delay in his childhood. There was no family history of psychiatric illness or mental retardation. None of the family members had phenotypic similarities with the patient. The patient had been suffering from psychiatric illness for the last 15 years. His predominant symptoms included suspiciousness, delusions of reference and persecution, second person auditory hallucination giving derogatory comments on the patient, and occasional irritability. His symptoms were waxing and waning in nature, without full remission in between the exacerbation of symptoms. The patient was earlier treated by various psychiatrists with Trifluoperazine, Haloperidol, Quetiapine, and Valproate. The patient had partial improvement with the above-mentioned medications, but due to the side effects the patient had discontinued them. On physical examination the patient was pale, head circumference was 54 cms, height was 160 cms, weight was 60 kg, and vitals were stable. His physical anomalies included spiky hair, bushy eyebrows, synophrys, prominent supraorbital ridge, low set ears, long eyelashes, prominent nose, open mouth, carries in teeth, talon cusp (in the right upper canine), broad thumbs and toes, camptodactaly of little finger, cervical hyperkyphosis, and scoliosis. His intelligence quotient (IQ) score was 60, suggestive of mild mental retardation. On investigation, an x-ray of the lateral skull showed prominent occipital protuberance, an X-ray of the bilateral hands and feet revealed broad terminal phalanges, and echocardiography was within normal limits. His hemoglobin was 8.8 gm%, red blood cell (RBC) count was 2.38 millions / cmm, and peripheral smear was suggestive of dimorphic anemia. The patient was assessed using the MINI International Neuropsychiatric Interview (M.I.N.I. English version 6.0.0) and was diagnosed as having a lifetime psychotic disorder. It was further sub-classified as schizophrenia paranoid type as per DSM – IV TR. In the presence of classical physical anomalies he was also diagnosed as having RTS. The patient was started on Tab Risperidone 2 mg / day and gradually the dose was built up to 6 mg / day, in divided doses, over two weeks. The patient had extrapyramidal symptoms and was managed with Tab Trihexyphenidyl 4 mg / day. The patient was symptom-free after four weeks and started going to work. He is under regular follow-up for the last six months and he is asymptomatic.

Case 2

A 20-year-old male presented with altered behavior for the last six months. He is the third of the three siblings born of a non-consanguineous marriage among the parents. The patient had global developmental delay and poor academic performance. There was no family history of psychiatric illness or mental retardation. None of the family members had phenotypic similarities with the patient. The family members noticed that the patient had decreased social interaction, was suspicious that others may harm him, had occasional irritability, was not going to work, and was with poor personal care for the last six months. There were no associated depressive symptoms. On mental status examination, the patient had delusion of persecution and blunt affect. On physical examination the patient had broad thumbs and toes, parrot beak–shaped nose, long eyelashes, widows' peak, synophrys, low set ears, deep palate, and malformed dentition, with talon cusp (Upper lateral incisor). His IQ score was 62, suggestive of mild mental retardation. The patient was assessed using the MINI scale and diagnosed as having a lifetime psychotic disorder. He was also diagnosed as having RTS in view of the presence of physical anomalies. He was started on Tab Amisulpride 100 mg / day, which was later increased to 200 mg / day in divided doses. The patient showed significant improvement after three weeks. He is on regular follow-up for last four months and has reached a pre-morbid state.

DISCUSSION

The two cases presented are the first cases described in literature about the association of schizophrenia / non-affective psychosis with RTS. Genetic analysis was not done due to unavailability. Schizophrenia is a complex neurodevelopmental disorder with a polygenic inheritance pattern. The analysis of genes potentially associated with schizophrenia is based on the observation that hypoxia prevails in the embryonic and fetal brain, and that interactions between the neuronal genes, molecular regulators of hypoxia, such as, hypoxia-inducible factor 1 alpha (HIF1A), and intrinsic hypoxia, occur in the developing brain and may create conditions for complex changes in neurodevelopment.[7] De Luca A *et al*., have evaluated the PC2 glutamine / Q-rich-associated protein (PCQAP) gene, which maps within the DiGeorge / velocardiofacial syndrome (DGS / VCFS) interval, as a potential candidate for schizophrenia susceptibility. The PCQAP encodes for a subunit of the large multiprotein complex PC2, which exhibits a coactivator function in RNA polymerase II mediated transcription. It is a case control study involving schizophrenia patients ($n = 378$) and controls ($n = 444$). The results indicate a possible involvement of the multiprotein complex PC2 in schizophrenia susceptibility.[8] The cAMP signal cascade is implicated in the intracellular events mediated by various neurotransmitters and studies have shown abnormalities in the components of cAMP signaling in schizophrenia.[9] The CREB protein is one of the messenger molecules involved in intracellular signal transduction pathways, used by most dopamine and serotonin receptor subtypes. In addition, CREB stimulates the expression of a number

of genes, alterations in the expression of which may be associated with schizophrenia.[10]

Petrij *et al*., showed that the breakpoints at 16p13.3, demonstrated in patients with RSTS, are all restricted to a region that contains the gene for the human CREB protein, a nuclear protein participating as a coactivator in cAMP-regulated gene expression.[11] The genes responsible for both the CREB binding protein and EP300 are considered to be key regulators of RNA polymerase II-mediated transcription, acting as transcriptional coactivators in the regulation of gene expression through various signal transduction pathways. Both are potent histone acetyltransferases.[3] The CRRB and EP 300 have also been identified as co-activators of HIF1A.[12] The factors discussed herewith, such as, regulators of RNA polymerase II and HIF1A may be some common etiological factors for the association of schizophrenia or non-affective psychosis and RTS.

CONCLUSION

Schizophrenia / non-affective psychosis can be a comorbid psychiatric condition with RTS. In future the genetic analysis of such cases would help in the clear understanding of a complex disease like schizophrenia.

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