Genetic Workup of Childhood Onset Psychosis Reveals Novel Neurodevelopmental Disorder: A Case Report

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Background

Childhood-onset psychosis is a rare and profoundly challenging mental health condition, marked by the emergence of psychotic symptoms before the age of 13 (1). Unlike adult-onset psychosis, childhood-onset psychosis can be more severe and debilitating and can be difficult to recognize when it is comorbid with neurodevelopmental conditions (2, 3). In addition, childhood onset psychosis shares genetic overlap with both adult onset psychosis and earlier-onset neurodevelopmental disorders such as autism spectrum disorders (3,4). This case highlights the identification of a newly identified neurodevelopmental disorder (NDD) and likely cause of childhood onset psychotic symptoms.

Case Description

A 15 year old caucasian female was admitted to our inpatient child and adolescent psychiatric unit with severe aggression, self-injurious behaviors features of psychosis. Psychotic symptoms included response to internal stimuli, and egodystonic derogatory auditory and visual hallucinations of children telling her to hurt herself and others. Psychotic symptoms emerged were accompanied by regression of previous emotional, behavioral, and cognitive functioning including depression, social anxiety and anhedonia. Interestingly, patient had cessation of pubertal development with amenorrhea around time of symptom onset. Episodes of agitation associated with disinhibition (uncharacteristic shouting at family, hitting and biting herself) were so functionally impairing that she was unable to attend the therapeutic school she was transferred to over the course of her illness. Psychotic symptoms were not responsive to antipsychotic medications and aggression was typically worsened due to hyperphagia. On admission, Bush Francis rating was only positive for hyperkinetic movements and automatic obedience, attempts to titrate ativan led to worsening irritability and agitation.

- Developmental history: premorbid borderline intellectual functioning, hypotonia, scoliosis, motor milestone delays.
- Family history: no known psychiatric disorders. Father in special education when younger.

Initial medical workup at outside institutions (EEG, MRI, chromosomal microarray analysis, TSH/thyroid antibodies, ceruloplasmin, ANA, serum anti-NMDA) was not consistent with an inflammatory or autoimmune etiology of psychosis. **Based on developmental history, lack of response to antipsychotic medications, and atypical, severe presentation, genetic evaluation was pursued. The final whole exome sequencing revealed a pathogenic variant of the SRCAP gene that is clinically distinct from Floating Harbor Syndrome (FLHS) which is affected by the same gene.**

Discussion

Chromatin remodelers and other epigenetic regulators play a central role in multiple neurodevelopmental processes. As a result, genetic mutations in the genes encoding these regulators frequently lead to NDDs. SRCAP, a gene responsible for encoding the SNF2-related CREBBP activator protein, is a crucial component of the SRCAP chromatin remodeling complex. Pathogenic mutations in SRCAP can lead to FLHS, a recognizable NDD characterized by distinctive craniofacial features, speech and language delay, short stature, and often intellectual or developmental delays (5). As of 2014, approximately 100 cases of FLHS have been reported in the medical literature. However, some of these individuals do not fit the classical description of FLHS and were found not to carry mutations in the SRCAP gene (6).

In 2021, Rots et. al describe **non-Floating Harbor Syndrome SRCAP-related NDD** as a condition resulting from variation in the SRCAP gene that is associated with behavioral and psychiatric problems, including psychosis (6). Of the 33 patients identified in this cohort, 66.7% had a history of intellectual disability or special education placement, 55% presented with behavioral problems and 12% demonstrated symptoms of psychosis. Psychiatric and behavioral features of this non-FLHS SRCAP related disorder can include developmental delay, mild intellectual disability, autism spectrum disorder, ADHD, psychosis, schizophrenia and tics with Tourette syndrome. Other features reported include joint hypermobility, scoliosis, pectus, chronic pain and facial features distinct from FLHS. Test results of our patient indicated that this condition was inherited from her father in an autosomal dominant manner although he did not overtly exhibit the physical or psychiatric characteristics of this condition.

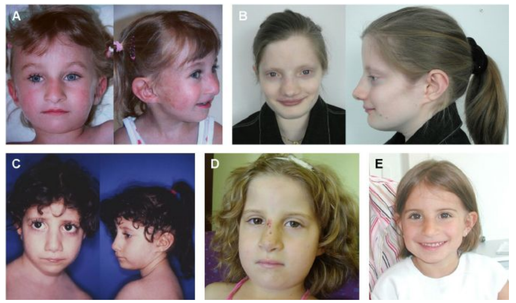

Figure 1: FLHS Phenotype

Figure 2: Non-FLHS SRCAP related NDD Phenotype

Conclusions

While genetic testing is not often part of the initial psychosis evaluation in children, it should be strongly considered given the overall low prevalence in this age group and influence of genetic and epigenetic factors in mediating psychosis (3,4,7). In addition, diagnosis of neurogenetic syndromes may have important implications for potential medical and neurologic comorbidities within a syndrome (4,7).

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