Case Report

Hallermann-Streiff Syndrome and Psychosis: A Case Report

Tarvis Peacock, MD[1]; Ubaid Khokhar, MD[1]; Jaclyn Murphy, BS[2]; Zach Murphy, BS[2]

Author affiliations are listed at the end of this article.

Correspondence to:
Tarvis Peacock, MD
Orange Park Medical Center
2001 Kingsley Avenue
Orange Park, FL 32073
(tarvis.peacock@hcahealthcare.com)

Abstract

Description

Hallermann-Streiff syndrome is a rare genetic congenital disorder, with fewer than 200 cases reported to date, that is characterized by brachycephaly with frontal bossing, micrognathia, a "bird-like" beaked nose, microphthalmia with congenital cataracts, dental abnormalities, hypotrichosis, skin atrophy, and short stature. There is limited data on psychosis in individuals with Hallermann-Streiff syndrome; the information available depicts mania rather than psychosis. This case report reviews the presentation and treatment of psychosis in a 32-year-old male with Hallermann-Streiff syndrome who was involuntarily admitted to an inpatient psychiatric unit for persecutory delusions and hallucinations. The patient's psychosis responded well to risperidone with a resolution of psychosis and suicidal ideation in 6 days. Psychosis in individuals with Hallermann-Streiff syndrome appears to respond to a high-potency second-generation antipsychotic. Given this patient's early onset of psychosis and limited social/occupational impairment, it is unclear if psychosis is a component of Hallermann-Streiff syndrome or if he has comorbid schizophrenia or schizoaffective disorder, bipolar type.

Keywords

Hallermann's syndrome; Hallermann-Streiff syndrome; psychosis; hallucinations; oculomandibulodyscephaly; craniosynostoses; schizophrenia; psychotic disorders; congenital abnormalities

Introduction

Hallermann-Streiff syndrome is a rare congenital disorder first described as oculomandibulodyscephaly in 1948 by Hallermann and then in 1950 by Streiff.[1] Fewer than 200 cases have been reported to date. The syndrome is characterized by brachycephaly (a wider, flattened skull) with frontal bossing (prominent forehead), micrognathia (small lower jaw), a "bird-like" beaked nose, microphthalmia (small eyes) with congenital cataracts (in 90% of cases), dental abnormalities, hypotrichosis (lack of body hair), skin atrophy, and short stature (**Figure 1**).[2,3] Narrowing of the upper airway is associated with the craniofacial configuration and can predispose affected individuals to early pulmonary infection, swallowing difficulties, respiratory insufficiency, obstructive sleep apnea, and greater general anesthesia risks.[4] Intellectual disability may present in a small subset of patients.[2] Data on mental disorders in individuals with Hallermann-Streiff disorder is extremely limited, and the information available appears to describe mania rather than psychosis.[5] This case report discusses the manifestations and treatment of psychosis in a 32-year-old male with Hallermann-Streiff syndrome.

Case Description

A 32-year-old Caucasian male with Hallermann-Streiff syndrome, deafness of unknown etiology, and history of schizophrenia presented for psychiatric evaluation after his transfer from a freestanding emergency department. He was found on a bench by EMS with an

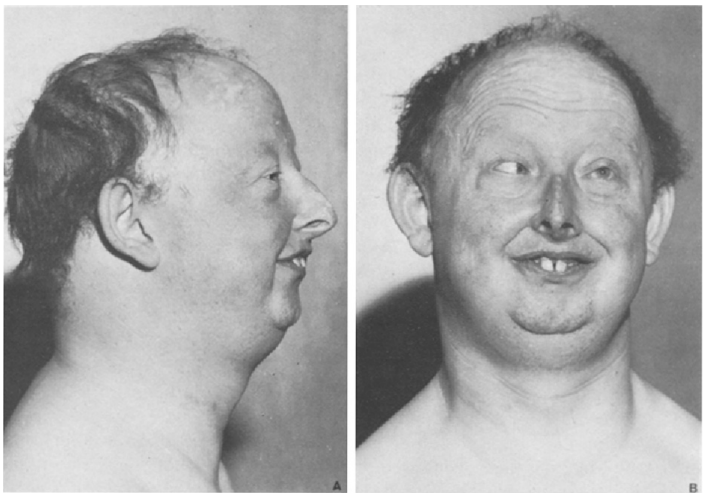

Figure 1. Reprinted by permission from Springer Nature: *Springer Journal of Neurology* Crevits L, Thiery E, vander Eecken H. Oculomandibular dyscephaly (Hallermann-Streiff-François syndrome) associated with epilepsy. *J Neurol*. 1977 Sept; 215: 225–230. https://www.springer.com/journal/415

altered mental status. He was subsequently evaluated and determined to be medically stable for involuntary psychiatric admission for acute psychosis. The emergency room clinician described the patient as delusional and suicidal, who believed spirits were encouraging him to self-harm. The patient reported that he had been having auditory, visual, and tactile hallucinations of spirits intermittently for the past 2 years, which had been worsening over the past week. No new known stressors were contributory. He reported that the auditory hallucinations commanded him to harm himself and others. He reported visual hallucinations of an old male, animals, and children. He also felt spirits stabbing and sticking him and expressed persecutory delusions of spirits harming him. During mood disorder screening, he endorsed neurovegetative symptoms of hypersomnolence "to keep [the] spirits away" and poor energy levels. He reported fair concentration, but he stated that the spirits attempt to distract him. He denied changes in appetite or feelings of guilt. He endorsed periods of increased energy, decreased need for sleep, and increased talkativeness caused by the "bad spirits waking me up and bothering me," which have lasted 4-5 days. He did not have elevated or irritable mood, racing thoughts, distractibility, and risk-taking behavior at this time; these subclinical hypomanic episodes were not related to comorbid substance use.

Prior to his arrival at the current facility, the patient reported drinking 12 shots of whiskey to alleviate the auditory hallucinations. However, his blood-alcohol level was unremarkable. His urine drug screen was negative for amphetamines, barbiturates, methadone, benzodiazepines, cocaine, opiates, phencyclidine, cannabinoids, and methylenedioxymethamphetamine (MDMA). His complete blood count, thyroid-stimulating hormone, and complete metabolic panel were within normal limits.

The patient reported being diagnosed with schizophrenia 1 year ago with the onset of auditory hallucinations at age 14 and had been without antipsychotic medication for 4 months. It appeared the patient was homeless and using illicit substances since his diagnosis, thereby contributing to medication nonadherence. The patient may have lost insurance/disability benefits while he was incarcerated, which further restricted his access to care. Previous medications included nightly sertraline 25 mg orally and doxepin 150 mg orally along with a monthly injection of paliperidone palmitate 134 mg. He also recognized aripiprazole tablets, but he was unable to recall his prior response to the treatment. It was unclear, based on his recollections, if his symptoms were more responsive to antipsychotic or antidepressant medication, or if he experienced worsening symptoms with antidepressant medications.

He had 1 prior suicide attempt via overdose on alprazolam due to his fear of spirits. He reported 1 previous hospitalization for acute psychosis (hallucinations of spirits and persecutory delusions).

Collateral information from his mother revealed that the patient had a transient lifestyle as well as a history of crack cocaine and cannabis use. His last date of use of either drug was unknown. The patient was described as displaying some callous and unemotional traits, including abuse and torture of animals, during childhood. His mother reported that he developed auditory hallucinations at age 14, which worsened with later illicit substance use. His developmental history of risks for and prodromal symptoms of psychosis was otherwise unclear due to family factors, including a mother with deafness and other communication limitations. The chronology of his symptom development in relation to puberty is unknown. One could speculate the patient might have experienced puberty between ages 12-15, but the onset is unclear. The usual signs of adrenarche (development of adrenal hormone-related secondary sex characteristics) are masked by the hypotrichosis (lack of hair) associated with the patient's syndrome. There was no known family history of psychosis. He completed high school and attended college without learning difficulties. Over time, his relatives described antisocial personality traits emerging, leading to estrangement from his family. He was not on Supplemental Security Income and did not have Medicaid or Medicare insurance.

During the initial encounter, he was alert and oriented to people, the time, and his situation. His mood was described as scared and his affect appeared constricted and anxious. He seemed to have high intellectual functioning with fluent use of American Sign Language. His thought processes appeared to be linear and without loosening of associations. His thought content was significant for voices commanding him to harm himself, but he denied suicidal and homicidal ideations verbally (although reported suicidal ideation on the rating form). His attention and concentration were adequate. His insight and judgment were limited.

The differential diagnoses included unspecified psychotic disorder, schizophrenia, major depressive disorder (recurrent, severe, with mood-congruent psychotic features), bipolar II disorder (current episode depressed, with psychotic features), schizoaffective disorder, alcohol-induced psychotic disorder, and psychotic disorder due to Hallermann-Streiff syndrome.

Due to a history of positive response but current inability to afford a long-acting second-generation antipsychotic, the patient was started on oral risperidone. The risperidone was titrated to 6 mg daily (as 3 mg twice daily) for 6 days with the resolution of psychosis and suicidal ideation. Adverse effects included mild shoulder rigidity that improved with benztropine 1 mg orally twice daily. His Brief Psychiatric Rating Scale (BPRS) score decreased from 65 to 41. Changes in specific domains are described in **Table 1**. Of note, the post-treatment BPRS represents symptoms measured 4 days after discharge with self-reported medication non-adherence. Patient Health Questionnaire (PHQ)-9 score was 17 (in the moderately severe range) on admission. No post-discharge PHQ-9 was available. The patient was stabilized and discharged with a recommendation to follow up at a local community mental health center.

Discussion

There have been reported cases of variants of Hallermann-Streiff syndrome involving psychiatric and neurodevelopmental anomalies, such as manic episodes and complete agenesis of the corpus callosum, respectively.[2,5,6] However, this patient's case is aberrant given the presence of hallucinations and delusions without concurrent manic symptoms.

This patient was clinically diagnosed with Hallermann-Streiff syndrome, one of the world's rarest syndromes, in his early childhood based on brachycephaly, frontal bossing, microphthalmia, vision defects, dental abnormalities, hypotrichosis, and short stature. He later developed auditory hallucinations during adolescence with no known genetic predisposition for psychotic disorders. A diagnosis of schizophrenia was given in early adulthood by an out-of-state provider. It is indeterminate if his psychosis is related to Hallermann-Streiff syndrome or a separate pathology.

Hallermann-Streiff syndrome is hypothesized to be caused by a *de novo* mutation, possibly

Table 1. Brief Psychiatric Rating Scale Pre- and Post-Treatment (BPRS) Scores.

Scores indicate the following severity: 0 = not assessed, 1 = not present, 2 = very mild, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = severe, and 7 = extremely severe.

BPRS Domains	Pre-Treatment Score	Post-Treatment Score*
Somatic concern	3	1
Anxiety	6	4
Depression	6	4
Suicidality	4	1
Guilt	1	1
Hostility	1	1
Elevated mood	1	1
Grandiosity	1	1
Suspiciousness	2	2
Hallucinations	7	5
Unusual thought content	7	2
Bizarre behavior	2	1
Self-neglect	6	1
Disorientation	1	1
Conceptual disorganization	1	1
Blunted affect	5	4
Emotional withdrawal	3	3
Motor retardation	2	1
Tension	1	1
Uncooperativeness	1	1
Excitement	1	1
Distractibility	1	1
Motor hyperactivity	1	1
Mannerisms and posturing	1	1
Total score	**65**	**41**

*Post-treatment BPRS represents symptoms measured 4 days after discharge with self-reported medication nonadherence.

involving gene GJA1—a gene responsible for making connexin 43.[2,7] However, genetic testing currently does not play a role in diagnosis and heritability is unclear. A diagnosis is made from physical characteristics and symptoms alone. The treatment is not curative but rather involves managing the individual manifestations of the syndrome. For example, surgery may be required for craniofacial defects. Speech and occupational therapy may be provided to improve functional limitations related to the malformations.[2]

Psychosis in this individual with Hallermann-Streiff syndrome responded to a second-generation antipsychotic. Given this patient's early onset of psychosis (age 14 per mother) and relative lack of social/occupational impairment, it is unclear if psychosis is a component of Hallermann-Streiff syndrome or part of early-onset comorbid schizophrenia. Typical risk factors for schizophrenia include multiparity, small size for gestational age, late winter birth, and bleeding during pregnancy.[8] Multiparity and late winter birth were absent in this patient. Decreased fetal measurements

and increased maternal blood volume loss are unknown biological factors in this patient but it should be noted that these factors are associated with a three- to four-fold increased risk of schizophrenia in males.[8]

Future areas for research should explore genetic links between Hallermann-Streiff syndrome and schizophrenia as well as distinct genetic causes of Hallermann-Streiff syndrome. To date, karyotyping, single exone sequencing, array comparative genomic hybridization and trio genome sequencing have been unable to identify causative mutations and/or genes associated with Hallermann-Streiff syndrome. [9]

Limitations in this study include lack of access to brain imaging, an unclear longitudinal course of symptoms since adolescence, a limited knowledge of previous mood symptoms, and class effects of medications (ie, response to previous antipsychotics, adverse effects of antidepressants).

Conclusion

Risperidone was well-tolerated, documented as effective, and appears to be a viable treatment option for psychosis associated with Hallermann-Streiff syndrome. It is important to connect patients with community resources such as community mental health centers with case management to provide an early bridge to medication treatment, to potentially include long-acting injectables, and psychosocial follow-up with hope for better access and compliance. Future research should explore genetic links between Hallermann-Streiff syndrome and psychotic disorders, and special attention should be given to concurrent mood symptoms.

Conflicts of Interest

The authors declare they have no conflicts of interest.

Drs Khokhar and Peacock are employees of Orange Park Medical Center, a hospital affiliated with the journal's publisher.

This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

Author Affiliations

1. Orange Park Medical Center, Orange Park, FL
2. Edward Via College of Osteopathic Medicine – Auburn Campus, Auburn, AL

References

1. Thomas J, Ragavi BS, Raneesha P, et al. Hallermann-Streiff syndrome. *Indian J Dermatol*. 2013;58(5):383-384. doi:10.4103/0019-5154.117311
2. Hallermann-Streiff Syndrome. Genetic And Rare Diseases Information Center (GARD). https://rarediseases.info.nih.gov/diseases/288/hallermann-streiff-syndrome. Updated April 10, 2020. Accessed January 31, 2022.
3. Crevits L, Thiery E, van der Eecken H. Oculomandibular dyscephaly (Hallermann-Streiff-François syndrome) associated with Epilepsy. *J. Neurol*. 1977;215(3):225-230. doi:10.1007/BF00312481
4. Cohen MM Jr. Hallermann-Streiff syndrome: a review. *Am J Med Genet*. 1991;41(4):488-499. doi:10.1002/ajmg.1320410423
5. Narayanan HS, Mohan KS, Manjunatha KR, Channabasavanna SM. An unusual variant of Hallermann-Streiff syndrome. *Indian J Psychiatry*. 1985;27(2):159-162.
6. Sigirci A, Alkan A, Bicak U, Yakinci C. Hallermann-Streiff syndrome associated with complete agenesis of the corpus callosum. *J Child Neurol*. 2005;20(8):691-693. doi:10.1177/08830738050200081101
7. Pizzuti A, Flex E, Mingarelli R, Salpietro C, Zelante L, Dallapiccola B. A homozygous GJA1 gene mutation causes a Hallermann-Streiff/ODDD spectrum phenotype. *Hum Mutat*. 2004;23(3):286. doi:10.1002/humu.9220
8. Hultman CM, Sparén P, Takei N, Murray RM, Cnattingius S. Prenatal and perinatal risk factors for schizophrenia, affective psychosis, and reactive psychosis of early onset: case-control study. *BMJ*. 1999;318(7181):421-426. doi:10.1136/bmj.318.7181.421
9. Schmidt J, Wollnik B. Hallermann-Streiff syndrome: a missing molecular link for a highly recognizable syndrome. *Am J Med Genet C Semin Med Genet*. 2018;178(4):398-406. doi:10.1002/ajmg.c.31668