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CASE SERIES

PREMATURE GRAYING OF HAIRS IN PATIENTS OF SCHIZOPHRENIA SPECTRUM DISORDER, AN INCIDENTAL FINDING OR SOME ASSOCIATION BETWEEN THESE TWO ENTITIES: A CASE SERIES.

Keywords: *Oxidative stress, premature graying of hair, schizophrenia, psychosis*

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ABSTRACT

Introduction:
Healthy hair is a sign of general well-being and youth. This case series addresses the unique occurrence of premature graying of hair (PGH) in patients diagnosed with schizophrenia spectrum disorder. PGH is perceived as a prominent sign of aging, driven by oxidative stress, which may indicate underlying systemic oxidative stress and be associated with various progressive systemic illnesses, including neuropsychiatric disorders.

Case Presentation:
In this case series, 14 young individuals (aged 18-25 years) exhibited heterogeneous behavioral symptoms suggestive of schizophrenia spectrum disorder alongside premature graying of hair. Behavioral symptoms included social withdrawal, unprovoked anger outbursts, auditory hallucinations, and significant socio-occupational dysfunction. Additionally, some cases had a family history of psychotic disorders or past medical conditions such as seizure disorders.

Result:
Patients were diagnosed with schizophrenia spectrum disorder by a dermatologist after excluding other cutaneous and systemic causes of graying. Behavioral changes varied in duration but commonly led to socio-occupational dysfunction, prompting medical attention. The onset of PGH ranged from simultaneous to before or after the behavioral disturbances, suggesting a possible timeline of progression linked to oxidative stress.

Conclusion:
Oxidative stress appears to be a common factor in both schizophrenia spectrum disorder and premature graying of hair, potentially serving as an early indicator of schizophrenia. Early intervention targeting oxidative stress and inflammatory markers, along with current therapeutic measures, may improve prognosis. Premature graying of hair could be considered a red flag for future schizophrenia transition, warranting further research to validate this association and explore preventive measures.

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INTRODUCTION

Premature graying of hair (PGH) is often dismissed as a cosmetic concern, but recent studies suggest it may signal deeper health issues, particularly in young individuals. The phenomenon of PGH involves the loss of pigment in hair follicles due to the decline in melanocyte activity [1]. Typically associated with aging, PGH's occurrence in individuals under 30, especially in those with underlying health conditions, raises intriguing questions about its etiology and implications.

Schizophrenia spectrum disorders (SSDs) are severe psychiatric conditions characterized by chronic and debilitating symptoms, including hallucinations, delusions, and cognitive impairments. The onset of SSDs usually occurs in late adolescence or early adulthood, a critical period for personal and social development. Emerging research indicates a potential link between PGH and SSDs,

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suggesting that premature graying may serve as a biomarker for oxidative stress and systemic inflammation, both of which are implicated in the pathophysiology of schizophrenia.

Oxidative stress, defined as an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify these harmful byproducts, plays a crucial role in both PGH and schizophrenia. Studies have shown that increased oxidative stress can damage melanocytes, leading to premature hair graying. Similarly, oxidative stress is thought to contribute to the neurodegenerative processes underlying schizophrenia, where excessive ROS damages neural cells and impairs cognitive function [2].

Recent studies have highlighted that individuals with schizophrenia exhibit higher levels of oxidative stress markers and lower levels of antioxidants, which could explain the premature aging phenomena, including PGH, observed in these patients. For instance, a study found significant associations between oxidative stress markers and symptom severity in schizophrenia, suggesting that oxidative damage might play a pivotal role in the disease's progression [3]. Additionally, a review emphasized the potential of oxidative stress as a therapeutic target for early intervention in schizophrenia, further underscoring the relevance of PGH as a possible early indicator of the disorder [4].

In this case series, we present young individuals clinically diagnosed with SSDs, who also exhibit PGH. This dual presentation is rare and warrants further investigation to determine whether PGH could be an early, visible marker for SSDs. Identifying such markers is crucial for early diagnosis and intervention, which can significantly improve patient outcomes. By exploring this unique association, our study aims to contribute to the growing body of evidence linking dermatological and psychiatric conditions, potentially paving the way for novel diagnostic and therapeutic strategies.

PATIENT INFORMATION

Table 1: Case series (a)

Cases	Age (Years)	sex	Clinical presentation	Duration of Behavioral Changes	Duration Of PGH	Family History of Psychiatric Disorder	Past Psychiatry /Medical History	Substance History
1	20	Male	Social withdrawal, self-isolation, avoiding daylight, excessive rumination about resentful scenes and feelings, suspiciousness and hostility, mild idea of reference, vague and transient AH with socio-occupational dysfunction, and diminished biological drives.	12-14 months, increased from the last 5 days	8-9 months	h/s/o psychotic disorder in father.	Not - significant	Tobacco smoking
2	23	Male	Unprovoked anger outbursts, aimless wandering talking to animals and self, intermittent episodes of laughter and crying, persecutory delusions, brief intermittent AH calling his names and at times commanding him, increased appetite with disturbed sleep with significant socio-occupational dysfunction.	14-16 months increased from the last 1 month.	2 years	Not-significant ant	Not - significant	Chew tobacco
3	24	Female	Unprovoked anger, extreme fear, view some devil with black clothes inside water, at times, wandering without clothes. Muttering to self, inappropriate smile, 3rd person AH, resulted in socio-occupational dysfunction.	02-03years increased from last 1year	03-04years	Not-significant	Not-significant	Chew tobacco

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Table 2: Case series (b)

Cases	Age (Years)	sex	Clinical presentation	Duration of Behavioral Changes	Duration Of PGH	Family History of Psychiatric Disorder	Past Psychiatry /Medical History	Substance History
4	19	Female	Emotional hypo responsiveness, not relying on being questioned, odd behavior like drinking excessive water, spitting here and there, throwing objects like mirrors, watches, and utensils in which patient views his reflection on the road with blunted affect and poor self-care with socio-occupational dysfunction.	06-05months, increased from the last 10 days	03-04months	h/s/o psychotic disorder in elder brother.	Not-significant	Not significant
5	20	Male	Self-isolation, social withdrawal, hypervigilance, suspiciousness, emotional turmoil, a vague sense of her thoughts being known by others, blunted affect, the idea of reference, and persecution with socio-occupational dysfunction.	08months increased from the last 15 days	1year	Not significant	h/o seizure disorder and on anti epileptic drugs from the last 5 years	Tobacco smoking
6	18	Male	Repetitive blinking of the eyelid up to 32 to 36 per minute, Verbal and physical hostility towards family members, inappropriate laughter at times, fear of being monitored, idea of reference, vague persecutory ideations, poverty of content of speech, with socio-occupational dysfunction.	04 months, increased from the last 7 days	03- 04 months	h/s/o psychotic disorder in grand-mother (maternal side)	Not significant	Not significant

Table 3: Case series (c)

Cases	Age (Years)	sex	Clinical presentation	Duration Of Behavioral Changes	Duration Of PGH	Family History Of Psychiatric Disorder	Past Psychiatry /Medical History	Substance History
7	20	Male	Inappropriate smile and self-muttering, social withdrawal, commanding and commentary AH, disturbed sleep and appetite with socio-occupational dysfunction.	6 months, increased from last 15-20 days	6 months	Not-significant	Not-significant	Not-significant
8	19	Male	Odd behavior like repeated making abnormal clicking sounds from mouth followed by self-smiling and self-	1 year increased from last 4-5 days	6 months	Not-significant	Not - significant	history of cannabis use present

			muttering, inappropriate affect disturbed sleep and appetite with socio-occupational dysfunction.					
9	24	Male	The feeling of insecurity, vague feeling of being followed, exaggerated emotional reactions to ordinary life events, eating only self-cooked food, circumstantial speech, being confined to a room, disturbed sleep and appetite with socio-occupational dysfunction.	10 to 12 months, increased from the last 1 month	1 year	h/s/o psychotic disorder in father	Not - significant	Not-significant

Table 4: Case series (d)

Cases	Age (Years)	sex	Clinical presentation	Duration Of Behavioral Changes	Duration Of PGH	Family History Of Psychiatric Disorder	Past Psychiatry /Medical History	Substance History
10	25	Male	Social withdrawal, occasional suspiciousness toward family members, and at work workplace he would remain isolated, blunted affect, poverty of content of speech, normal sleep and appetite with socio-occupational dysfunction.	18 to 20 months, increased from the last 15 days.	2 years	Not-significant	Not - significant	Not - significant
11	25	Male	Odd gestures like rubbing genitals in public places, sitting alone in the corner of the room, staring at the wall, and at times talking to self loudly, inappropriate effect, disturbed sleep and appetite with socio-occupational dysfunction.	04 months, increased from last 03-04 days	06-08 months	Not-significant	Not significant	Not significant.
12	25	Female	Social withdrawal, poor self-care, fearfulness, episodes of anger outburst, blunted affect, poverty of content of speech, disturbed sleep and appetite with socio-occupational dysfunction.	06 months increased from the last 15 days.	06 months	Not-significant	Not - significant	Not - significant

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Table 5: Case series (e)

Cases	Age (Years)	sex	Clinical presentation	Duration of Behavioral Changes	Duration Of PGH	Family History of Psychiatric Disorder	Past Psychiatry /Medical History	Substance History
13	23	Female	Mid-night awakening and peeping through the window, suspiciousness, unprovoked anger, standing for hours in open space and talking to the self, idea of reference, disturbed sleep, and appetite with socio-occupational dysfunction.	06-08 months, increased from last 7 days	06-08 months	h/s/o post partumpsychosis, 2 years back, resolve on treatment	Not significant	Not significant
14	24	Male	Remain suspicious and fearful, poor emotional response, blunted affect normal sleep and appetite with socio-occupational dysfunction	1 year increased for 1 month	14 to 16 months.	Not -Significant	Not-significant	Tobacco smoking, history of cannabis use present
PGH-Premature graying of hair, h/s/o- history suggestive of, AH- auditory hallucination								

CLINICAL FINDINGS

In this case series, we examined 14 patients aged 18 to 25 years who presented with premature graying of hair (PGH) and behavioral symptoms indicative of schizophrenia spectrum disorder. The clinical findings revealed diverse symptoms including social withdrawal, self-isolation, suspiciousness, hostility, unprovoked anger outbursts, aimless wandering, inappropriate laughter and crying, visual and auditory hallucinations, and significant socio-occupational dysfunction.

These symptoms varied in duration and severity, with behavioral changes often preceding or coinciding with the onset of PGH. Several patients had a family history of psychiatric disorders, such as psychotic disorders in their parents or grandparents, while others had personal histories of medical conditions like seizure disorders or substance use, including tobacco and cannabis. The findings suggest a potential link between oxidative stress, as evidenced by PGH, and the development of schizophrenia spectrum disorders. In several cases, PGH began simultaneously with or shortly after the onset of behavioral symptoms, highlighting oxidative stress's role in the pathophysiology of both conditions.

TIMELINE

Historical Information

- **Case 1:** Behavioral changes began 12-14 months ago, and PGH started 8-9 months ago.

- **Case 2:** Behavioral changes started 14-16 months ago, PGH began 2 years ago.

- **Case 3:** Behavioral changes started 2-3 years ago, PGH began 3-4 years ago.

- **Case 4:** Behavioral changes began 6-5 months ago, and PGH started 3-4 months ago.

- **Case 5:** Behavioral changes started 8 months ago, PGH began 1 year ago.

- **Case 6:** Behavioral changes began 4 months ago, and PGH started 3-4 months ago.

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- **Case 7:** Behavioral changes began 6 months ago, PGH started 6 months ago.

- **Case 8:** Behavioral changes began 1 year ago, PGH started 6 months ago.

- **Case 9:** Behavioral changes began 10-12 months ago, PGH started 1 year ago.

- **Case 10**: Behavioral changes began 18-20 months ago, PGH started 2 years ago.

- **Case 11**: Behavioral changes began 4 months ago, and PGH started 6-8 months ago.

- **Case 12:** Behavioral changes began 6 months ago, PGH started 6 months ago.

- **Case 13:** Behavioral changes began 6-8 months ago, and PGH started 6-8 months ago.

- **Case 14:** Behavioral changes began 1 year ago, PGH started 14-16 months ago.

Current Episode of Care

- Medical attention sought for socio-occupational dysfunction.
- Behavioral changes led to the diagnosis of schizophrenia spectrum disorder.

DIAGNOSTIC ASSESSMENT

Diagnostic testing included clinical evaluation by psychiatrists and dermatologists to confirm schizophrenia spectrum disorder and exclude other causes of premature graying. Laboratory tests, including oxidative stress markers, and imaging studies were performed to support the diagnosis. Challenges encountered included distinguishing PGH as a marker of oxidative stress from other etiologies and correlating it with the onset of psychiatric symptoms.

THERAPEUTIC INTERVENTIONS

Upon identifying the 10 males and 4 females with unusual behavioral symptoms and PGH, therapeutic interventions were initiated. These included antipsychotic medications to manage schizophrenia symptoms, antioxidant supplements to address oxidative stress, and counseling to support socio-occupational functioning. The administration of therapeutic interventions varied, with antipsychotic dosage tailored to symptom severity and antioxidant supplements given daily. Changes in therapeutic interventions were made based on patient response, with adjustments in medication dosage and the introduction of cognitive behavioral therapy for improved outcomes.

Follow-up and Outcomes

Follow-up was conducted to assess clinical and patient-reported outcomes. Most patients showed improvement in socio-occupational functioning and a reduction in behavioral symptoms. Follow-up diagnostic tests indicated stabilization of oxidative stress markers. Intervention adherence was generally high, with patients tolerating the treatments well. Adverse events were minimal, with some patients experiencing mild side effects from antipsychotic medications. The presence of PGH and its association with oxidative stress and schizophrenia highlights the need for ongoing monitoring and early intervention to improve patient outcomes.

DISCUSSION

In this case series, we focused on 14 subjects (10 males and 4 females) aged 18 to 25 years, all exhibiting a heterogeneous group of unusual behavioral symptoms along with premature graying of hair, symptoms suggestive of schizophrenia spectrum disorder. Notably, cases 1, 4, 6, and 9 had a genetic risk factor for psychotic disorders; case 13 had a history of a psychotic episode; case 5 had a history of seizure disorder; and cases 8 and 14 experienced behavioral disturbances followed by the intake of psychoactive substances (cannabis), increasing their vulnerability to schizophrenia.

In all cases, medical attention was sought due to disturbances in socio-occupational functioning, although behavioral changes began much earlier. A common feature in all cases was the predominance of premature graying of hair. For cases 6, 7, 9, 12, and 13, hair graying started simultaneously with behavioral changes, while for cases 2, 3, 5, 10, 11, and 14, graying preceded behavioral disturbances. Conversely, cases 1, 4, and 8 experienced hair graying after behavioral disturbances.
Oxidative stress, implicated in the pathogenesis of schizophrenia, appears to be a central factor. It may lead to maternal immune activation during pregnancy, releasing pro-inflammatory cytokines and overproducing kynurenic acid, an N-methyl-D-aspartate receptor (NMDAR) antagonist, resulting in NMDAR hypofunction and thus negative and cognitive symptoms of schizophrenia. This NMDAR hypofunction also leads to glutamate disinhibition by GABAergic interneurons, causing hyperactivity of dopaminergic pathways in the brain and positive symptoms of schizophrenia.

Additionally, catecholamines like dopamine and norepinephrine auto-oxidize to generate free radicals, further decreasing glutathione (GSH), a major antioxidant, exacerbating NMDAR hypofunction. Increased oxidative stress also destroys melanocytes, leading to premature graying of hair. Thus, oxidative stress links schizophrenia's pathophysiology and premature graying of hair. Evidence suggests that increased oxidative state, dysfunctional antioxidant capacities, and increased inflammatory cytokines play roles in psychiatric disorders' pathogenesis. However, quantitative assessment of ongoing oxidative stress in the brain remains challenging.

Early signs of schizophrenia can appear years before onset, and identifying at-risk individuals early can improve prognosis. Yet, current instruments for detecting prodromal symptoms and predicting psychosis transition remain controversial. This case series suggests premature graying of hair could be a red flag for future schizophrenia, warranting early intervention and treatment.

Premature graying of hair (PHG) is a phenomenon where hair loses its pigment before the age of 20 in Caucasians, 25 in Asians, and 30 in Africans. The etiology of PHG is multifactorial, involving genetic, environmental, and physiological factors. A case-control study was conducted to evaluate epidemiological and biochemical variables associated with PHG. They found significant associations with atopic diathesis, sedentary lifestyle, family history, smoking, and stress. Lower levels of serum calcium, ferritin, Vitamin B12, and HDL cholesterol were observed in PHG cases [5]. Research studied the association between PHG and osteopenia in a North Indian population. They found no significant difference in bone mineral density (BMD) between individuals with and without PHG, suggesting no strong correlation between PHG and osteopenia [6].

A study found significant associations between PHG and family history, iron deficiency, and family history of depression. Smoking and herpes simplex virus infection showed negative associations with PHG. They also observed significant associations between PHG and irritable bowel syndrome in Caucasians and heart disease in Asians [7]. A study on the association between PHG and metabolic risk factors was conducted. They found that individuals with PHG had higher waist circumference, blood pressure, and fasting blood sugar levels, along with lower HDL cholesterol, indicating a link between PHG and metabolic syndrome [8]. A study assessed the serum levels of iron, copper, and calcium in patients with PHG. They found reduced levels of these trace elements in PHG patients, with significant correlations between the severity of PHG and serum iron and calcium levels [9].

A study evaluated oxidative stress markers in PHG patients. They found higher levels of malondialdehyde (MDA) and lower levels of antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), suggesting oxidative stress plays a role in PHG [10]. Research studied the impact of PHG on the quality of life in the Western Indian population. They found that PHG significantly affected self-esteem and social interactions, often leading to psychological distress and the need for medical and psychological intervention [12].

Clinical implications

A candidate having premature gray hair serves as a good candidate for early schizophrenia intervention and can be easily detected before transition. A novel approach can be using oxidative stress and inflammatory markers as a target for schizophrenia progression by boosting exogenous antioxidants along with current therapeutic measures. Various new technologies and robust studies are required for further understanding of earlier phenotypical changes like premature graying of hair, repetitive blinking of eyelids, or increased blink rate to enable us to target clinical symptoms and identify preventive measures to halt the transition to schizophrenia in high-risk individuals.

Declaration of Conflicting Interests

The author declared no potential conflicts of interest concerning the research, authorship, and /or publication of this article.

Declaration of Patient Consent

The author certifies that all patients were included in this case series only after explaining the study to the patients/next of kin/caregiver and subsequently obtaining written informed consent, In the form, the patient and caregiver have given consent for his/ her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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