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Review

Marie Antoinette Syndrome

Ahmetcan Kurt[1], Fehmi Balandi[1], Oytun Erbaş[1,2]

ABSTRACT

Marie Antoinette syndrome (Canities subita) can be defined by the sudden graying of a person's hair as a result of extreme stress, trauma or an illness. It was named after Marie Antoinette, the French queen whose hair turned white overnight until she was guillotined in 1793 during the French Revolution. Marie Antoinette, who was dethroned by the revolution, she knew that she would be executed by a guillotine, so her hair suddenly turned white while in prison due to excessive stress. Cases of sudden graying due to stress and trauma have been documented many times since over 200 years. These cases have been classified in terms of area affected, age, gender, cause of illness, and concomitant diseases, and were named Marie Antoinette syndrome for the first time in 2009. In Latin, it has been named Canities subita by using the words' ani (subita) and whitening (Canities). Although its molecular mechanism has not been clearly resolved, various hypotheses have been put forward by researchers. These are related to the rapid destruction of pigments in the hair, abnormalities that have occurred in the scalp, or the mechanisms of body defense cells that affect pigment oogenesis. Marie Antoinette syndrome, which is a very rapid whitening of hair, eyelashes, eyebrows or other body hair, can be triggered by bodily illnesses, severe psychological illnesses, emotional stress or severe trauma caused by an event. Nowadays, data on this disease are limited, and it is a subject open to research for the medical world.

Keywords: Canities subita, hair bleaching, marie antoinette syndrome, melanogenesis.

In a story mentioned in the Talmud in the Journal of the Royal Society of Medicine published in 2008, in 83 AD, an 18-year-old student's hair turned completely white overnight, as a result of hard and stressful work. This case is the first recorded example of Canities subita.[1,2]

Another story also known is Sir Thomas More, an English writer and lawyer, whose hair turned gray overnight before his execution in the Tower of London. For this reason, it is also called Thomas More syndrome. More recent studies have shown that some people who survived the bombardment during World War II experienced this type of sudden hair graying.[3,4]

Before Mary, the Scottish queen, was executed in 1587 at the age of 44, the executioner is said to have shown her head and her hair was completely white due to the stressful times she spent in prison.

According to an incident reported in the British Medical Journal in 1902, the right pubic hair of a 22-year-old woman who had menstruation turned white after witnessing an execution scene. However, during the doctors' examination, interestingly, they have observed that pigments were still present in the hair on the left side. In addition, her menstruation has stopped for 9 months.

Another example is Shah Jahan, architect of the famous Taj Mahal. Due to the troubled process he experienced as a result of the death of his beloved wife Mumtaz Mahal in his arms, it was reported that his hair turned completely gray after two weeks.[5]

King of France, III. Henry's (1553-1610), St. After the Bartholomew's day massacre, it is rumored that his hair turned white overnight. Although no

[1]ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Turkey
[2]Department of Physiology, Medical Faculty of Demiroğlu Bilim University, Istanbul, Turkey

Correspondence: Ahmetcan Kurt. Deneysel Tıp Enstitüsü, 41470 Gebze-Kocaeli, Türkiye.

E-mail: ahmetcankurt_1999@hotmail.com

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certainty has yet been reached, III. It is known that Henry's life was spent in wars.[6]

British doctor and journalist Francis Edmund Anstie, who had severe neuralgia attacks, reported that his eyebrows and the right part of his hair turned white. However, a few days after the neuralgia attacks, the hair color was returning to its original state. Anstie emphasized that there was no alopecia and that he observed this case in a few more patients. Viktor Urbantschitsch, an Austrian doctor, found that hair graying after episodes of neuralgia, without any specific brittleness or alopecia of the hair. However, in his case, it was stated that the hair color change was permanent.

In 1977, Canities subita was extensively investigated in a 58-year-old female patient. The case stated that he saw white strands in his hair within a period of 3 months, the bleaching started first in the middle part of the head and after rapid spread, all the hair turned gray, except for a region around the head. Dermatological diseases such as total hair loss and vitiligo have not been reported in the patient. When the history of the patient was investigated, it was stated that he had asthma in his childhood and was treated for goiter. She started menstruating for the first time at the age of 16, but entered the menopause phase at 39. She also had bladder stone surgery at the age of 39, and it was stated that she used drugs such as diazepam in the past. Now, It has been determined that she is in good general health. In the examination on the scalp, the area consisting of pigmented hair has been created in the center of formed a circular area and there was only graying in the hair. In the study, samples were taken from the patient's pigmented and non-pigmented hair and blood cells, immune system cell numbers were calculated using biochemical methods. When the blood values of the patient were examined, no abnormality was detected. No damage or inflammation was detected in the blood vessels. However, when the hair follicles were examined, it was seen that they were not at their original length. In April 1980, in the second biopsy scan taken from the area where hair loss was most intense, it was seen that the majority of the hair follicles were in the anagen phase and no alopecia areata disease was found. Interestingly, the patient's hair was restored to its original state in about two years. In immunofluorescence microscopic scans, IgM (Immunoglobulin M) and IgG (Immunoglobulin G) were detected in the follicular epithelial cells of the patient. Based on these results, the idea that whitening might be an auto immunological mechanism was proposed.[7] The most famous example is Marie Antoinette, for which he is also named. With the French Revolution, he was executed by guillotine in 1793 at the age of 38. Marie Antoinette's hair turned white overnight, like that of a 70-year-old woman, who spent the last days of her life in prison. In reference to this event, in 2009 an article was named as Marie Antoinette syndrome. However, today it is used for Canities subita seen in women. Thomas More syndrome is used for Canities subita seen in men.[3-8]

MELANOGENEZ

Dark brown-black hair, which is found in the vast majority of the world's population, protects the scalp from sunstroke and is an important carrier for melanin salt balance. However, the remaining 5-10% of the world's population, mostly from Northern Europe, do not have dark brown-black hair due to mutations in the melanocortin-1 receptor (MC1R), a G-protein coupled receptor. Mutations in the MC1R gene are believed to contribute to white, blonde, and auburn hair color in individuals in less sunny climates in northern Europe, while natural selection pressures likely limited this mutation in sunny tropical regions.[9]

HAIR CYCLE

Hair follicles have their own stem cells in the scalp. Each hair follicle goes through about 10 to 30 reproductive cycles during its lifetime. The anagen (active growth) phase lasts for 2–8 years, the catagen (regression) phase for 4-6 weeks, and the telogen (rest) phase for 2–3 months.[10] Hair bleaching (canities) and shedding are one of the characteristic changes that occur in our body as we age. The production of melanin occurs in melanocytes originating from the neural crystal, and they interact with dermal papilla fibroblasts and matrix keratinocytes to provide pigmentation of the hair shaft.[11] The production of hair first begins with the formation of hair follicles, with mesenchymal cells located on the skin that originates from epidermal cells. In this stage called morphogenesis, as the follicle begins to grow, it takes the shape of a rod. In the meantime, large amounts of growth factor are synthesized. The central hair shaft (HS), which includes the cuticle, cortex and medulla, which is the innermost part of the hair, begins to develop at this stage, and Henley and Huxley cylindrical layers IRS (inner root sheath) surround the HS layer. Later, the

dermal papilla (DP) consisting of the mesenchymal cell community becomes permanent by wrapping around the hair follicle, thus surrounding the hair follicle.

In the anagen phase, the proliferating matrix cells begin to migrate upward. The migrating cells surround the HS and IRS layers. They cover layers of Henley, Huxley and cuticle (IRS), cuticle, cortex and medulla (HS) from the outside to the inside. While HS layer cells are composed of keratin filaments rich in cysteine amino acids that give the hair its flexible and durable structure, IRS layer cells provide a support and protective environment to the hair shaft during growth and differentiation. In the catagen phase, which is the regression or regression phase, differentiation stops. Epithelial cells attached to the outer root sheath (ORS) are rapidly dragged into apoptosis. The hair follicle reaches an equal or shorter radius with the whole hair. Dermal papillae have been found as attached to epithelial cells.

In the telogen phase, the hair goes into the resting phase. No apoptosis, differentiation or division occurs. In the exogenous phase, hair shedding occurs.[12,13]

HAIR BLEACHING

Human hair follicles contain two types of melanin: the black-brown pigment eumelanins are mostly found in black and brown hair, and yellow or red pheomelanin are found in auburn and blonde hair. The production of melanin (melanogenesis), the pigment that gives hair its color, begins to decrease with age. Melanosome complexes, a cytoplasmic organelle produced by melanocytes originating from the melanin in the hair, cause hair bleaching by breaking down melanins through a series of biochemical pathways using the tyrosinase enzyme. One of the reasons for melanocyte aging is the accumulation of mutations in nuclear and mitochondrial DNA resulting from reactive oxygen species and thus apoptosis of cells.[14] In gray hair, the pigmented part and the non-pigmented part (white) are found as mixed. The chemical composition and water content of the hair strands in these parts show differences.[15]

According to the observations made by the neurologist Charles-Édouard Brown-Séquard, he had plucked off a beard that the ends of which were whitened. The next day, he noticed that new whitened beards were growing, and he repeated this procedure for 5-6 weeks. He observed that the newly emerged white hairs completely grow in 2-5 days.

In the same period, as a result of microscopic examinations made by Pincus on the hair of women of different ages, it was observed that the graying of the hair generally starts from the base of the hair. This is because pigment production stops in the scalp and hair grows without pigmentation. In addition, Pincus observed that the white parts of the hair were swollen and inside filled with air. As a result, color change occurred with the entry of air into the already pigmented area.

Later on, in studies conducted by Naegeli on the bleaching of women's hair, it was observed that bleaching can start both at the base of the hair and at the end of the hair and can progress rapidly up to 1 cm in 2 days. In other words, a hair strand could be white completely in a few weeks.[16]

CANITIES SUBITA (MARIE ANTOINETTE SYNDROME)

Canities subita is the whitening of the hair or other body hair by losing its color in a very short time. Canities subita, poliosis and piebaldism are associated with vitiligo, telogen effluvium (hair loss), alopecia areata and psychiatric disorders.[17]

Since the early 1800s, researchers have come across a total of 196 Canities subita cases as a

Table 1. Statistics related to the cases (n=196)[2]

Affected region	
Hair	170
Eyebrow	22
Eyelash	30
Beard	19
Other	10
Reason	
Aging or no noticeable cause	21
Body diseases	39
Psychiatric illnesses	10
Emotional stress	126
Other indicators	
Alopecia	23
Poliosis	58
Vitiligo	9
4-18 yaş	22

result of a literature review in English, German, Italian, French and Spanish. In only 44 of the cases, by the physicians themselves (confirmed case), their patients had sudden whitening. 82 cases were identified claiming to have sudden bleaching (unconfirmed case). The existence of 33 cases has not been clarified. The cases were evaluated with factors such as the affected areas and the causes of the disease (Table 1).

HYPOTHESES

Hypotheses have been created by researchers for the causes of Canities subita occurrence from different times and places.

1. **Pigmentophage:** Nobel medical prize-winning microbiologist Élie Metchnikoff suggested in her article published in 1902 that sudden hair whitening is the defense cells called 'pigmentophage' that are produced in the hair medulla and phagocyte pigments.[18] However, the existence of such cells has not been detected.
2. **Bubble in the hair shaft:** Pinu annulati (PA) was described for the first time in the article published by Leonard Landois in 1866. In this condition, when the hair shafts were examined, it was seen that the distribution of keratin was not homogeneous and there were dark bands and gaps in the hair when viewed in light. Like an optical illusion, regions with air gaps have been seen white in light.[19]
3. **Hair dyes:** Another reason for Canities subita is the hypothesis that "Canities subita onset is observed in hair dyed with temporary hair dyes". In 1907, before the use of Paraphenyldiamine (PPD) as hair dye, temporary hair dyes, either herbal or chemical, such as henna, chamomile, silver, lead, were used. The use of temporary dyes can be used to explain some cases before 1907. However, it is insufficient to explain the current cases.[20]
4. **Alopecia areata:** Alopecia areata is an autoimmune, dermatological disorder that causes hair loss on the scalp and hair follicle loss. Hair loss may occur in a certain area (patchy alopecia areata) or hair loss may occur on the entire scalp (alopecia totalis). It can be seen in other body parts, but it is often observed on the scalp. There are also cases of alopecia (Alopecia universalis) causing hair loss on the whole body. Studies have shown that the presence of alopecia does not depend on age, gender and ethnic identity, and it has been observed that it affects approximately 0.1-0.2% of the population in the society. Alopecia can be seen simultaneously with many autoimmune diseases such as thyroid disorders and diseases such as depression, anxiety, psoriasis and vitiligo.[21,22] Alopecia areata is an organ-specific T cell-mediated disease that targets hair follicles. Peribulbar lymphocytic infiltration, disrupting the normal hair cycle, is considered to be the main pathophysiological mechanism responsible for the disease process. Normal hair cycle is disrupted in alopecia areata; Dystrophic changes in anagen follicles, rapid progression of hair follicles from anagen to catagen and as a result telogen phases (shedding) are observed. With a genome-wide study, certain individual genes can be identified that may represent increased susceptibility to alopecia areata. When the whole genome was researched, 139 single nucleotide polymorphisms (SNPs) associated with alopecia areata have been determined. The study showed that the genomic regions containing the CTLA4, IL2/IL21, IL2RA and Eos genes that regulate the proliferation of inflammatory cells are susceptibility loci for alopecia areata.[23,24] This disease can occur with sudden alopecia and may leave pigmented hair white overnight.[20]
5. **Piebaldism and poliosis:** Piebaldism is an autosomal, dominant dermatological disease characterized by the absence of melanocytes in a certain part of the skin or hair. It appears in combination with a white skin (leucoderma) devoid of melanocytes and white hair (poliosis) In the majority of patients, it is seen as a depigmented white hair area just above the forehead. They occur in the neural crest during embryonic development as a result of faulty migration of melanocytes, and the most common cause of the disease is the KIT proto-oncogene located in the 4q12 region and mutations in the SNAI2 gene. Scientists have identified 14 point mutations, 9 deletions, and 2 nucleotide-splice mutations that cause piebaldism. KIT mutations at the 4q12 locus lead to abnormal melanocyte migration and

an absence of melanocytes in the ventral midline of the epidermis. In addition, it has been observed that mutations in the SNAI2 gene located at the 8q11.21 locus, which is the transcription suppressor of E-cadherin, lead to piebaldism. Histopathological observations made in the affected areas showed that the area was pigment-free. Vitiligo, albinism and Waardenburg syndromes can be used as a differential factor in the diagnosis of piebaldism. In approximately 30% of detectable cases, piebaldism and Canities subita are seen simultaneously.[25,26]

6. **Vitiligo:** Vitiligo is a depigmentation disease seen in 0.5 to 2% of the world population. Polymorphisms that occur in genes related to immune response and melanogenesis occur as a result of oxidative stress, interruption of cell communication and metabolic abnormalities.[27] The most important symptom of vitiligo is depigmentation in certain areas of the skin and its mottled appearance. Depigmented areas are mostly the face, scalp, arms, knees and fingers, and the hairs in these areas are also depigmented. Even if it does not cause a painful condition in general, a painful condition can occur in sunburn. Different hypotheses have been proposed regarding the occurrence of vitiligo. These include the autoimmune hypothesis, which includes destruction of melanocytes by macrophages and dendritic cells against various cellular damage and reactive oxygen species, the neural hypothesis based on the development of nerve damage that interacts with melanocytes and releases melano cytotoxic substrates, and the destruction of melanocytes by cytotoxic agents formed in melanogenesis is the destruction (self-destruction) hypothesis.[28,29] However, compared to vitiligo alopecia and poliosis, Canities subita was seen at a lower rate.

7. **Telogen effluvium:** Telogen effluvium is a dermatological disease characterized by excessive hair loss that causes alopecia areata, causing hair cycle disruption as a result of drug use, vitamin and mineral deficiency, disease, hormonal imbalance, stress or trauma, and environmental factors. It was first described in 1961. It is more common in women than in men, and there is no distinction between races. American dermatologist Kligman, who first described the disease, stated that this disease developed with the early termination of the anagen phase of the hair follicles. The hair follicle, which stops growing in the anagen phase, passes to the catagen phase and then to the telogen phase. For the treatment of the disease, chemicals such as beta-blockers that inhibit the exogenous-catagen phases or stimulate the anagen phases can be used. For the reinforcement, minerals such as zinc and iron, which are necessary in the anagen phase, are used.[30,31]

Conclusion

Hair and body hair help us adapt to the outside world by performing a variety of functions from the moment we are born, including body temperature regulation, detoxification, sweating, and homeostasis. These pigment and protein-containing molecules exhibit a wide range of variances, resulting in a wide range of color variations, particularly depending on our geographic location and ethnicity. The adaptation of these pigments to defend against UV radiation and severe heat, primarily from the sun, has been different in warm geographies than in cold geographies. Hair and body hair, which are made up of inert cells, have a limited lifespan before shedding and being re-synthesized by rooting out stem cells. Over time, the melanogenesis pathway ceases to work, resulting in the development of colored (white and grey) hair in older people. These extremely natural processes deteriorate due to a variety of circumstances, leading to abnormal hair loss and whitening at an early age. As a result of the immune system's poor operation, the hair cycle and melanogenesis, which are controlled by the immune system, face these abnormal situations. The vast majority of these cases are the result of large-scale stress or trauma impacting the immune system, or abnormalities in genes controlling the hair cycle and melanogenesis, according to research. The sudden hair whitening of Marie Antoniette, a legendary French queen who has been reported numerous times throughout history, has attracted the scientific world's interest. However, due to a lack of cases and scientific studies, the molecular process has yet to be fully resolved. Several theories have been proposed in relation to disorders like vitiligo and psoriasis, which impair skin and hair

pigmentation, or early bleaching as a result of pigment breakdown caused by cellular stress. Understanding the disease's molecular mechanism will be a sign of hope for those seeking treatment.

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