UDC 616.594.14-031.81-053.2

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Clinical case of alopecia totalis in pediatric practice

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Modern Pediatrics. Ukraine. (2023). 4(132): 99-103. doi 10.15574/SP.2023.132.99

For citation: Stroi OA, Kyian TA, Balatska NI, Levadna LO, Kozynkevych GE. (2023). Clinical case of alopecia totalis in pediatric practice. Modern Pediatrics. Ukraine. 4(132): 99-103. doi 10.15574/SP.2023.132.99.

Alopecia (baldness) is a pathological hair loss. A chronic relapsing course leads to a violation of the emotional sphere of the child, worsens the quality of life. Alopecia is considered autoimmune, since it is characterized by hair loss due to lymphocytic infiltration around the hair follicles. It can be secondary as a result of infectious and inflammatory processes.

Purpose — is to conduct own clinical observation of a child with total alopecia to increase the awareness of doctors about this pathology in children.

Clinical case. The article presents a clinical case of total alopecia in an 11-year-old child. It is known from the anamnesis that in 9 months the child began to lose hair on his head, at 2 years old — eyebrows and eyelashes, at 3 years old he was diagnosed with total alopecia. The patient had a complex clinical and laboratory examination with the involvement of a multidisciplinary team, since alopecia can occur under the mask of autoimmune diseases and immunodeficiencies.

Total alopecia, atopic dermatitis, changes in immunological status in the anamnesis, cases of early mortality among family members, as well as a history of alopecia areata in the father gave us reason to suspect a genetic disease in the patient, including autoimmune polyendocrinopathy candidiasis-ectodermal dystophia (APECED syndrome) with mutation in the AIRE gene.

Conclusions. For verification the diagnosis and choose a treatment strategy, the patient needs an additional examination: sequencing of the relevant locus of the AIRE gene to detect mutations characteristic of APECED syndrome, as well as a serological test to detect the titer of antibodies to Candida and a puncture biopsy of the scalp. Considering the above, the prognosis for recovery is unfavorable. The research was carried out in accordance with the principles of the Declaration of Helsinki. Informed consent of parents was obtained for the study.

No conflict of interests was declared by the authors.

Keywords: alopecia, autoimmune polyendocrine syndrome (APECED), immunodeficiency, treatment, obesity.

Клінічний випадок тотальної алопеції в педіатричній практиці

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Алопеція (облисіння) — це патологічне випадіння волосся. Хронічний рецидивний перебіг цього захворювання призводить до порушення емоційної сфери дитини, погіршує якість життя. Алопеція вважається аутоімунною, оскільки випадіння волосся відбувається через лімфоцитарну інфільтрацію навколоволосяних фолікулів, також може бути вторинною внаслідок інфекційних і запальних процесів. Дотепер не розроблено протокол лікування алопеції, заснований на принципах доказової медицини.

Мета — навести власне клінічне спостереження за дитиною з тотальною алопецією для підвищення обізнаності лікарів щодо цієї патології в дітей.

Клінічний випадок. Наведено клінічний випадок тотальної алопеції в дитини віком 11 років. З анамнезу відомо, що в 9 місяців у дитини почало випадати волосся на голові, у 2 роки — брови і вії, у 3 роки встановлено діагноз тотальної алопеції.

Пацієнтові проведено комплексне клініко-лабораторне обстеження із залученням мультидисциплінарної команди, оскільки алопеція може перебігати під «маскою» аутоімунних захворювань та імунодефіцитів.

Тотальна алопеція, атопічний дерматит, зміни в імунологічному статусі в анамнезі, випадки ранньої смертності серед членів родини, а також історія гніздової алопеції в батька дали підстави запідозрити в пацієнта генетичне захворювання, у тому числі аутоімуну поліендокринопатію кандидозно-ектодермальну дистофію (синдром APECED) з мутацією в гені AIRE.

Висновки. З метою верифікації діагнозу та вибору тактики лікування пацієнт потребує додаткового обстеження: секвенування відповідного локусу гена AIRE для виявлення мутацій, характерних для синдрому APECED, а також серологічного дослідження для виявлення титру антитіл до *Candida* та пункційної біопсії шкіри голови. Враховуючи вищевикладене, прогноз одужання несприятливий. Дослідження виконано відповідно до принципів Гельсінської декларації. На проведення дослідження отримано інформовану згоду батьків дитини.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: алопеція, аутоімунний поліендокринний синдром (APECED), імунодефіцит, лікування, ожиріння.

Introduction

Alopecia (baldness) is a pathological hair loss. The term comes from the Latin word «alopex» — fox (wild foxes often have areas devoid of hair).

Alopecia in childhood is a serious medical and social problem, which is associated not only with an increase in the incidence among children and adolescents, but also with an increase in the frequency of severe forms of the disease, torpid to traditional methods of treatment therapy [7].

Chronic relapsing course of dermatosis leads to disruption of the emotional sphere of the child, neurotic disorders, social disadaptation, and significantly worsens his quality of life [3].

Total alopecia (alopecia totalis, or AT) is a heterogeneous multifactorial disease, which, according to morphological development, is one of the staged varieties of alopecia areata (alopecia areata, or AA), having common etiological factors [6].

AT is manifested by a complete loss of hair on the scalp and skin, where there is normal hair

growth [10]. Today it is considered autoimmune, since it is characterized by hair loss due to lymphocytic infiltration around the hair follicles. Also, the disease can be secondary against the background of infectious and inflammatory processes [3]. Patients with AT have a more severe course together with a worse prognosis for hair regrowth, and a less effective treatment [8]. The development of AT depends on genetic characteristics and environmental factors. The genetic predisposition has been established by observational studies of monozygotic twins. AA in monozygotic twins has similar onset times and hair loss patterns. Some patients with AA have a family history of the disease that spans several generations. From 4% to 28% of patients with AA have at least one family member with this disease [10].

Genetic susceptibility is evidenced by genome-wide association search (GWAS) data pointing to specific human leukocyte antigen genes associated with the development of AA.

Polymorphism of the human leukocyte antigen (HLA)-DRB1 is characterised by a number of autoimmune diseases, including aplastic anemia, systemic lupus erythematosus, Vogt–Koyanagi–Harada syndrome, and multiple sclerosis.

The polymorphism of the HLA-DRB1* 04 and HLA-DRB1* 16 alleles is associated with an increased risk of developing AA. There is data pointing to several polymorphisms that are more associated with AT — HLA-DRB1*1104 and HLA-DQB1*0301. In addition to genetic factors, the trigger for the development or relapse of the AT can be the diseases of an infectious nature, the use of drugs, as well as stress [9].

In general, the lifetime risk of developing AA is 1.7% (near 270 cases per 100,000 people). However, this value is lower for AT. AT affects nearly 0.03% per 100,000 people of the population. Children and adolescents suffer from AT more often than the other age groups [8,10].

The molecular mechanisms of pathogenesis are being studied; it is known that T-lymphocytes are responsible for the development of an autoimmune reaction in the case of AA and AT [1]. The main role in pathogenesis belongs to CD8+ T-lymphocytes; these cells produce interferon (IFN)-γ, which activates cytokines IL-2, IL-7, IL-15 and IL-21. IL-15, by suppressing regulatory T cells, ensures the proliferation of natural killers. In addition, cytokines activate transcription of the JAK/STAT signaling pathway. Patients with AA have overexpression of JAK3 [3,8].

Hair in the anagen period during histological examination is characterized by inflammatory reaction with the accumulation of lymphocytes in the bulbar part of the follicle, which resembles a «bee swarm». Eosinophilia may also be seen. The long-term development of the disease histologically indicates the presence of only telogen and catagen phases [9].

Diagnostics. Trichoscopy is used for diagnosis, which reveals perifollicular yellow or black spots, or the presence of vellus, or thinning hair. In case of difficulties with establishing a diagnosis, a histological examination is used. Usually, one or two 4 mm needle biopsies are performed to examine the specimens in detail [10].

Modern approaches to therapy. An analysis of international standards shows that a protocol for the treatment of AA based on the principles of evidence-based medicine has not yet been developed. The most effective treatments for AT include topical steroids, intralesional steroids, topical immunotherapy, phototherapy, pulsed systemic steroids, and immunosuppressants [5].

Phototherapy using a photosensitizing agent (psoralen), along with skin irradiation with long-wave ultraviolet radiation (PUVA) Psoralen Ultra-Violet A and photodynamic therapy (PDT), has been successfully used in severe forms of AA [1].

Alopecia may be a manifestation of immunological diseases, namely autoimmune polyendocrinopathy candidiasis-ectodermal dystophia (APECED), known as autoimmune polyendocrine syndrome type 1 (APS-1), which is a rare monogenic autosomal recessive disease. It is caused by mutations in the autoimmune regulatory (AIRE) gene, which is located on chromosome 21q22.3. AIRE is involved in the regulation of thymus T-cell tolerance to self-antigens and the removal of autoreactive cells. Impaired AIRE function leads to the production of many anticytokine and organ-specific antibodies and causes a severe autoimmune disease that affects several endocrine organs and other tissues. The diagnostic criteria for APECED include at least two pathological conditions (diagnostic dyad): chronic mucocutaneous candidiasis (CMC); hypoparathyroidism or Addison's disease (adrenal cortex insufficiency). Other endocrine or non-endocrine manifestations of APECED may include thyroid disease (autoimmune thyroiditis, Grave's disease), gastrointestinal manifestations (chronic active hepatitis, malabsorption, asplenia, juvenile pernicious anemia), dermatological diseases (alopecia, vitiligo), prima-

ry hypogonadism, kidney disease. Bowel dysfunction has been attributed to bacterial overgrowth, pancreatic insufficiency, lymphectasia, candida infection, and cholecystokinin deficiency. In rare cases, humoral immunodeficiency may occur [2,7].

According to the literature, hypoparathyroidism can appear before the age of 10 years, and adrenal insufficiency can appear before the age of 15 years. A correlation was also found with hypoparathyroidism and AA [2,4].

Since the role of AT as a manifestation of AA in the picture of the APECED syndrome has not yet been studied enough. The analysis of this clinical case may be useful for further study of the etiology and pathogenesis of AT, the patterns of manifestation of the APECED syndrome, as well as the development of effective methods for their correction [10].

Purpose of the study — to conduct own clinical observation of a child with total alopecia to increase the awareness of doctors about this pathology in children.

Clinical case

An 11-year-old patient was admitted to the children's department of the hospital in Kyiv with complaints of lack of hair growth of the scalp, eyebrows and eyelashes, periodic increase in blood pressure, periodic nosebleeds, overweight.

From the anamnesis it is known that the boy is from the 1st physiological pregnancy, the 1st birth. He was born at 42 weeks pregnancies; childbirth was rapid; at birth he had a slight asphyxia. He was breastfed for up to 6 months; he was vaccinated according to schedule. From mother's words, the child began to lose hair on his head from 9 months of age. At the age of 12 months all of his hair fell out from the scalp. His eyebrows and eyelashes fell out when he was 2 years old. At the age of 2, he was diagnosed with atopic dermatitis and insect allergy. At the age of 3 he was diagnosed with total alopecia. In anticipation of childhood, frequent severe acute respiratory syndrome (SARS) with obstructive laryngitis were observed. The patient lived in the village for 2 years of the Zhytomyr region with his grandmother. After 2 years he lived in Kyiv, where at the age of 9 his condition improved significantly: his eyebrows appeared. After visiting the village in summer, the eyebrows disappeared again.

From the family history it is known that the child's mother was born in the Zhytomyr region, Ovruch district — one of the most affected by the Chernobyl accident. She lived there until she was 15 years old. Mother's brother suffers from psoriasis. The mother's uncle died of pneumonia at the age of 5.

The father of the child often suffered from infectious diseases in childhood. At the age of 7 he was diagnosed with nested alopecia, for which he received treatment for 5 years. After it he fully recovered. Exacerbations of the disease were not observed. He connects the appearance of alopecia with the disaster at the Chernobyl nuclear power plant.

According to the results of an immunological research conducted in a child at the age of three, an increase in the number of free T-lymphocytes, CD16+-lymphocytes (killers), a decrease in IgA titers was revealed.

After that, the patient was not examined and treated, the parents re-applied for advice when the child was 11 years old.

AT, atopic dermatitis, changes in the immunological status in history, cases of early death among family members, as well as the history of nested alopecia in the father gave us a reason to suspect a genetic disease in the patient. This includes the APECED syndrome with a mutation in the AIRE gene, the ectodermal manifestations of which can be the enamel hypoplasia of permanent teeth, nail dystrophy, tympanic membrane calcification, and dermatological disorders (AA and vitiligo) [4]. As is known from the family history, early mortality was observed among the patient's family members, which is typical for APECED [8]. This may also indicate the possible inheritance of this syndrome in an autosomal recessive manner.

Thus, we carried out a complete clinical and laboratory examination of the patient and a multidisciplinary examination by such specialists: dermatologist, trichologist, endocrinologist, neuropathologist, gastroenterologist, nutritionist, pediatrician, immunologist and geneticist.

At the time of examination, the patient's height was 160 cm; weight was 68 kg; waist circumference was 91.5 cm; hip circumference was 100 cm; Body mass index (BMI) was 26.56. His blood pressure was 132/87; pulse was 65 beats/min.

The results of the tests showed that no changes were detected in the general blood test. The screening for hepatitis was negative. A significant number of results were within the normal range: total protein (71 g/l), total bilirubin (9.5 μmol/l), Alanine Aminotransferase (ALT)

Table 1

The results of a immunological examination (27th of May, 2021)

Immunoglobulins	Serum immunoglobulins, g/l	Reference values*, g/l
IgG	15.5	(7.3–13.5)
IgA	2.4	(0.9–2.6)
IgM	1.35	(0.6–1.6)

Note: *reference values for ages 10–11.

Table 2

The results of a comprehensive immunological examination (27th of May, 2021)

Cell population	Percent	Reference values* (%)	Quantity, µl	Reference values*, µl
Leukocytes	–	–	7203	(4700–8000)
Granulocytes	64.8	45–72	4670	–
Monocytes	4.9	2–9.5	351	–
Lymphocytes	30.3	(35–55)	2183	(1100–5900)
T-lymphocytes ($CD3^+$)	63.7	(60–76)	1391	(1200–2600)
Active $HLA\text{-}DR^+$	10.1	(<15)	140	–
$CD3^+ CD56^+$	0.7	(<12)	10	–
$CD4^+ CD8^+$	1.6	(<5)	22	–
$CD4^- CD8^-$	7.4	(<5)	103	–
T-helpers ($CD3^+ CD4^+$)	33.9	(31–47)	739	(650–1500)
Active ($HLA\text{-}DR^+$)	12.9	(3–13)	95	(40–120)
$CD56^+$	0.2	(<5)	2	–
T-cytotoxic ($CD3^+ CD8^+$)	29.2	(18–35)	638	(370–1100)
Activated ($HLA\text{-}DR^+$)	19.9	(6–29)	127	(40–270)
$CD56^+$	2.3	(<20)	15	–
Th/Tc ratio	1.2	(1.0–2.5)	–	–
B-lymphocytes $CD19^+$	16.1	(13–27)	351	(270–860)
B1A ($CD5^+$) Lymphocytes	38.8	(<20)	136	–
NK- lymphocytes ($CD3^- CD16^+56^+$)	19.7	(4–17)	429	(100–480)
$HLA\ DR^+$	21.3	(<25)	92	–
B-memory cells				
$CD19^+ CD27^+$	29.9	(13.3–47.9)	–	–
$CD19^+ CD27^+ IgD^+$	18.4	(4.6–18.2)	–	–
$CD19^+ CD27^+ IgD^-$	11.5	(8.7–25.6)	–	–
Timic migrants				
$CD45RA^+CD31^+ CD4^+$	32.7	(39–89)	241	(175–904)
αβ/γδ TCR				
CD3αβ	92.9	(83–97)	–	–
CD3γδ	7.1	(2–15)	–	–

Note: *reference values for ages 6–12.

(21 U/l), aspartate aminotransferase (AST) (33 U/l), Gamma Glutamyl TransPeptidase (GGTP) (13 U/l), urea (3.6 mmol/l), creatinine (55 µmol/l), cholesterol (3.94 mmol/l), serum cortisol (8.6 µg/dl), dihydrotestosterone (111 pg/ml), prolactin (2.5 ng/ml), *thyroid stimulating hormone* (TSH) (2.8 µM/ml), free T4 (0.89 ng /dl), antibodies to thyroperoxidase (3.3 IU/ml), glycosylated hemoglobin (5.1%), serum glucose (4.6 mmol/l).

Deficiency of 25 hydroxyvitamin D (69 nmol/l), low ferritin level (30.4 ng/l), slightly increased average blood glucose level (5.6 mmol/l), increased zinc (312 mg/dl) were found.

Tables 1 and 2 show the results of a comprehensive immunological examination.

Immunological data did not allow confirmation of APECED syndrome in the patient. Therefore, parents were asked to perform sequencing of the corresponding AIRE gene locus to identify

mutations specific to APECED syndrome, as well as serological testing to detect Candida antibody titer.

According to the results of an echocardiographic examination, no pathological changes were found. There were no heart diseases.

Expert consultations

Trichologist: AT.

Endocrinologist: alimentary-constitutional obesity of the 1st degree, impaired glucose tolerance. Arterial hypertension. Vitamin D deficiency.

Immunologist: AT, obesity due to excessive intake of energy resources, arterial hypertension.

Geneticist: AT, 50% genetic risk for siblings and offspring. There is no clinical data for syndromic pathology and chromosomal diseases.

Dermatologist: AT, to clarify the diagnosis and treatment tactics, a punch biopsy of the scalp is recommended.

Thus, alopecia in our patient appeared early, it had a chronic course. The patient never received any treatment. At the moment, he needs an expensive additional examination: sequencing of the corresponding locus of the AIRE gene to identify mutations specific to the APECED syndrome, as well as a serological study to detect the titer of antibodies to Candida and punch biopsy of the scalp. Given the above, the prognosis for recovery is unfavorable. According to the literature — The following conditions have been associated with alopecia areata: autoimmune Thyroid diseases (observed in 8–28% of patients), vitiligo (observed in 3–8% of patients), — these conditions do not respond well to treatment.

Conclusions

AT is a complex polyetiological multifactorial disease. A comprehensive examination of such patients with the involvement of a multidisciplinary team is necessary, since AT can proceed under the guise of autoimmune diseases and immunodeficiencies.

The choice of treatment method depends on the age of the patient, the duration of the disease, the propensity for treatment, as well as its cost.

Although there are many successful clinical treatments for alopecia, there is no a single Food and Drug Administration (FDA-approved) drug. The prognosis for long-term AT is unfavorable.

AT in children is a serious medical and social problem, the successful solution of which requires the participation of a psychologist. In some cases a wig is used.

No conflict of interests was declared by the authors.

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Стаття надійшла до редакції 11.02.2023 р., прийнята до друку 16.05.2023 р.