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REVIEW PAPER

ARTYKUŁ PRZEGLĄDOWY

UNDERSTANDING ABLEPHARON-MACROSTOMIA SYNDROME: FROM GENETICS TO MULTIDISCIPLINARY CARE

POZNANIE ZESPOŁU ABLEPHARON-MACROSTOMIA: OD GENETYKI PO KOMPLEKSOWĄ OPIEKĘ MEDYCZNĄ

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Summary

Ablepharon-Macrostomia Syndrome (AMS) is an exceedingly rare congenital disorder characterized by absence of eyelids (ablepharon) and enlargement of the mouth (macrostomia). Despite its rarity, understanding AMS is crucial for clinicians to provide comprehensive care. This review compiles current knowledge on AMS, emphasizing its genetic underpinnings and diverse clinical manifestations affecting various body systems. The syndrome is predominantly associated with mutations in the *TWIST2* gene, affecting embryonic mesenchymal cell development. Clinical symptoms encompass facial dysmorphia, ocular abnormalities, skin issues, and genitourinary anomalies. Diagnosis relies on clinical phenotype evaluation and genetic testing, often necessitating a multidisciplinary approach for optimal management. Surgical interventions, particularly for ocular and craniofacial anomalies, alongside symptomatic treatment, are pivotal in enhancing patients' quality of life. Psychological and

social support are integral components of care, fostering patient well-being and adaptation. Despite challenges, prognosis varies, with early diagnosis and holistic care potentially improving outcomes. This review underscores the importance of raising awareness among clinicians to facilitate early recognition and comprehensive management of this rare syndrome, ultimately promoting the well-being of affected individuals and families.

Keywords: Ablepharon-Macrostomia Syndrome, *TWIST2*, macrostomia, eye abnormalities, rare diseases

Streszczenie

Zespół Ablepharon-Macrostomia (AMS) jest niezwykle rzadkim wrodzonym zaburzeniem charakteryzującym się brakiem powiek (ablepharon) oraz powiększeniem ust (macrostomia). Pomimo swojej rzadkości, zrozumienie AMS jest kluczowe dla klinicystów w celu zapewnienia kompleksowej opieki. Niniejszy przegląd gromadzi aktualną wiedzę na temat AMS, kładąc nacisk na jego genetyczne podstawy i objawy kliniczne wpływające na różne układy ciała. Zespół jest głównie związany z mutacjami w genie *TWIST2*, wpływającymi na rozwój zarodkowych komórek mezenchymalnych. Objawy kliniczne obejmują dysmorfię twarzy, nieprawidłowości oczne, problemy skórne oraz anomalie układu moczowo-płciowego. Diagnoza opiera się na ocenie fenotypu klinicznego i testach genetycznych, często wymagających podejścia multidyscyplinarnego dla optymalnej opieki nad pacjentem. Interwencje chirurgiczne, szczególnie w obrębie zmian ocznych i w zakresie twarzy, wraz z leczeniem objawowym, są kluczowe dla poprawy jakości życia pacjentów. Psychologiczne i społeczne wsparcie stanowią integralne elementy opieki, wspomagając dobrostan pacjentów i ich adaptację. Pomimo wyzwań, rokowanie jest różne, a wczesna diagnoza i holistyczna opieka mogą potencjalnie poprawić wyniki. Niniejszy przegląd podkreśla znaczenie podnoszenia

świadomości wśród klinicystów, aby ułatwić wczesne rozpoznanie i kompleksowe zarządzanie tym rzadkim zespołem, ostatecznie promując dobrostan osób dotkniętych i ich rodzin.

Słowa kluczowe: Zespół Ablepharon-Macrostomia, *TWIST2*, makrostomia, anomalie oczne, choroby rzadkie

Introduction

Ablepharon-Macrostomia Syndrome (AMS) is a congenital disorder first described in 1977 [1]. Its name originates from two main phenotypic features of newborns with this syndrome, namely the absence of eyelids (ablepharon) and enlargement of the mouth (macrostomia) [2]. Its occurrence is extremely rare, resulting in limited general knowledge. Nevertheless, AMS, while its clinical presentation may cause anxiety, is a syndrome with a favorable prognosis [3].

In this review article, the current knowledge gathered on this rare disease is presented – its pathogenesis with an emphasis on genetic changes, as well as the clinical picture detailing various body parts. The multidimensional aspect of treating patients affected by this syndrome is also highlighted – from surgical interventions and symptomatic treatment to psychological support, bearing in mind a holistic approach to patient care.

Aim of the work

This review aims to consolidate and present the current understanding of AMS, a rare congenital disorder characterized by distinct phenotypic features, such as the absence of eyelids and an enlarged mouth. By delving into the pathogenesis with an emphasis on genetic mutations, particularly within the *TWIST2* gene, and providing a comprehensive clinical

picture, this review seeks to illuminate the multifaceted manifestations of AMS across various body systems. Furthermore, the review underscores the importance of a holistic treatment approach, integrating surgical interventions, symptomatic management, and psychological support. The overarching goal is to enhance awareness among clinical physicians and healthcare providers about AMS, promoting early diagnosis, effective management, and improved patient outcomes through interdisciplinary collaboration and support.

Methods

To prepare this article, resources available on the PubMed platform (https://pubmed.ncbi.nlm.nih.gov) were used. Given the limited number of articles on AMS, the selection criteria were quite liberal. To provide a comprehensive and exhaustive description of the condition, the authors made use of the few documented cases of this disease and the review articles that appeared over the years. For the purpose of this work, the keywords "Ablepharon Macrostomia Syndrome" were used to search for articles covering the period from 1977 (the year the disease was first described) to the present. Articles written originally in English or translated into English were selected.

Literature review results

Epidemiology

AMS is an extremely rare genetic disorder. The first case of this condition was described in 1977 [1]. Since then, fewer than 20 patients with AMS have been reported worldwide [2,4,5].

Recently, AMS was diagnosed in a newborn in Nigeria, marking the first reported case of its kind in the East African region [5].

Pathogenesis

The pathogenesis of AMS has been a mystery for researchers over the years. Initially, it was suggested that this extremely rare genetic disorder is inherited in an autosomal recessive manner [6,7]. However, in 2000, the first cases of familial occurrence were described, indicating autosomal dominant inheritance [8,9]. Subsequent research in later years confirmed this hypothesis [10]. On the other hand, in 2015, Marchegiani et al., based on genotype analysis of members of seven independent families affected by this condition, demonstrated that a mutation within the *TWIST2* gene is responsible for AMS [11]. *TWIST2* is a protein-coding gene that is located on 2q37.3. In the literature it may also appear under the names *DERMO1*, *DERMO-1* or *BHLHA39*. Its length is 62,450 base pairs (chromosome 2: from 238,848,085 to 238,910,534) and has 4 exons. It has 2 transcription variants (GenBank: NM_057179.2 and NM_001271893.2), which determine the formation of the same protein product, and another 3 predicted transcription variants related to miscellaneous RNA (GenBank: XR_007069137.1, XR_008485772.1, XR_008486261.1). Exome sequencing of AMS patients revealed a single missense mutation in the *TWIST2* gene, c.223G>A (E75K), which was associated with a change in the protein product (p.Glu75Lys) [12]. Protein encoded by *TWIST2* is a basic helix-loop-helix (bHLH) growth factor belonging to the *TWIST* protein family [12]. It has a crucial role in the development of mesenchymal cells during embryogenesis, significantly influencing the proper development of the skin and its appendages [13,14]. Additionally, TWIST2 is involved in epithelial-mesenchymal transition within the tumor microenvironment [15]. The *TWIST2* gene encoding protein consists of 160 amino acids, including two nuclear localization signals

(residues 29-32 and 52-56), a basic region (residues 66-77), a helix-loop-helix (HLH) domain (residues 78-118), and a twist box at the C-terminal end (residues 141-160). Through the HLH domain, *TWIST2* homo- or heterodimers can bind to promoters and regulatory regions of various genes. Mutations in *TWIST2* may lead to impaired DNA binding function, resulting in altered expression of different genes [16]. In the case of AMS, a missense mutation occurs within the basic domain of the TWIST2 protein. The amino acid p.Glu75 is substituted with lysine. Interestingly, mutations at the same site, but resulting in the appearance of glutamine or alanine in this location, are associated with the development of Barber-Say syndrome (BSS), which phenotypically resembles AMS [11]. Some authors have suggested that AMS and BMS actually represent one syndrome [17]. Cases of mosaic expression of *TWIST2* mutations have also been described. They typically manifest milder changes compared to typical cases of AMS or BSS [18]. Recently, using the Zebrafish model organism and a novel base editor, researchers successfully generated a *TWIST2* mutation [19]. Cases of overlapping focal facial dermal dysplasia (FFDD) type 3, also known as Setleis Syndrome (SS), with BBS and AMS have also been described. FFDDs are rare genetic skin disorders characterized by skin lesions clinically resembling scars. They can be bilaterally located in the case of FFDD 1-3 or in the preauricular area in the case of FFDD4 [20]. It has been reported that Setleis syndrome is caused by mutations within the *TWIST2* gene. Several nonsense mutations and missense mutations in the nuclear localization signal or bHLH domain of *TWIST2* have been described. These mutations most likely affect the dimerization process of *TWIST2*, resulting in impaired binding of *TWIST2* to various genes [21,22]. Furthermore, it has been shown that patients with nonsense mutations (c.486C>T [Q119X] and c.324C>T [Q65X]) within *TWIST2* had reduced levels of periostin in fibroblasts, a protein associated with cell adhesion and connective tissue development. This suggests that *TWIST2* also acts as an activator for the periostin gene [23]. Gene expression profiling in fibroblasts and lymphoblastoids from patients with SS has revealed a significant

role of *TWIST2* as both a DNA transcription activator and repressor. This enabled the identification of potential genes regulated by this transcription factor, which may influence the development of rare diseases caused by mutations in the *TWIST2* gene [24]. On the other hand, there have been cases of SS described where no changes were found within the *TWIST2* gene [25]. In three patients suffering from SS, a duplication of chromosome 1p36.22p36.21 was identified as the cause, while in one case, trisomy of chromosome 1p36.22p36.21 was implicated [25,26]. Recently, a case of SS was described where triplication of 1p36.23p36.22 was present [27]. The genetic defects responsible for the development of FFDD type 1 and type 2 still remain unknown. Mutations in *CYP26C1* are considered the cause of FFDD type 4 [28,29]. Ablepharon-Macrostomia-like Syndrome, as well as Hoffman syndrome and BILU (B-cell immunodeficiency, distal limb anomalies, and urogenital malformations) syndrome, have been associated with mutations in DNA Topoisomerase IIβ (TOP2B) [30]. A case of a patient exhibiting features of atypical AMS along with humoral immunodeficiency has been described [31,32]. Similar facial changes resembling eyelid underdevelopment and ocular hypertelorism observed in AMS and BSS are also seen in Sweeney-Cox syndrome, resulting from mutations in the basic DNA-binding domain of *TWIST1* [33,34].

Clinical symptoms

Head and face

AMS is a rare congenital genetic disorder characterized by numerous changes affecting the head, face, skin, and reproductive organs (Table 1). In infants with AMS, abnormalities in facial features are most commonly observed [2]. Particularly characteristic of this syndrome are eyelid developmental abnormalities, described as absence of eyelids (ablepharon) [6,35].

Indeed, the eyelid pathology involves the anterior lamella, which can make the term "ablepharon" misleading. Nonetheless, eyelid underdevelopment in patients with AMS is significant, often greater than in patients with BSS [2]. The abnormal development of the eyelids results in the inability to close them properly, leading to inadequate eye protection. Additionally, it often manifests as a lack of eyelashes and eyebrows or numerous, abnormal eyelashes [36]. Moreover, due to the absence of eyelids, defects in the meibomian glands can occur, leading to impaired tear film production and the presence of dry eyes. Due to significant eye exposure to damage, some patients may experience corneal opacity, vision disturbances, and photophobia [37,38]. In several cases, strabismus and squint have been reported [4,39]. AMS is additionally associated with other developmental disorders in the orbital region. The most common changes include hypertelorism, telecanthus, and periorbital fullness [9]. Cases of patients with a triangular head shape and flat occiput have been sporadically reported, although a normal head shape is usually observed [5].

Table 1. Clinical symptoms in AMS

Symptom	Description
Head and face	• Absence of eyelids (ablepharon) [6,35] • Inability to close eyes properly [18] • Lack of eyelashes and eyebrows or abnormal eyelashes [18] • Corneal opacity, vision disturbances, photophobia [37,39] • Strabismus, squint [4,39] • Hypertelorism, telecanthus, periorbital fullness [9] • Triangular head shape, flat occiput [5] • Macrostomia [40] • Cheek pads touching corners of mouth [40] • Narrow upper or lower lip, micrognathia, thick gums, cleft palate [35,37] • Triangular-shaped nose, broad bridge, wide nasal dorsum, malformed alar cartilages, underdeveloped and forward-directed nostrils [38,40] • Reduced size and low-set ears, altered shape, folding, fused earlobes [10,33]
Hair	• Sparse or absent hair on scalp, thinning hair with age [10]

	• Absent hair in pubic and axillary regions in adult patients [37]
Skin	• Redundant skin on hands, buttocks, feet, neck, around ears • Excessive dryness, laxity, prominent blood vessels • Early wrinkles, numerous furrows • Excessive skin pigmentation [35,37,39]
Mammae	• Absence or underdevelopment of mammary glands • Small nipples, complete absence, supernumerary nipples, wide nipple spacing [5,35]
Reproductive organs	• Ambiguous genitalia, micropenis, cryptorchidism, poorly developed scrotum resembling labia majora, absence of scrotum • Urethral opening in vaginal wall [1,33] • Male raised as female, normal menstruation later in life [35]
Other	• Tracheal stenosis (uncertain relation to AMS) [41] • Syndactyly, camptodactyly of fingers and toes [5,35] • Occasional lower level of intellectual development [6,39]

A typical symptom observed in AMS is macrostomia, characterized by wide mouth openings that are disproportionate to the size of the face. Disrupted tissue development in the facial region can lead to other abnormalities. One of the more common ones is the presence of cheek pads touching the corners of the mouth [40]. Less frequently described features include a narrow upper or lower lip, micrognathia, thick gums, and cleft palate. Dental abnormalities may involve wide tooth spacing, abnormal tooth shape, and midline shift [37]. In one patient, retrognathia and a congenital tooth were observed [40].

Patients with AMS often have a triangular-shaped nose and a broad bridge, which can be either low or high. In most cases, a wide nasal dorsum and a broad nasal tip are observed. The alar cartilages in almost all patients are malformed. Additionally, the nostrils are underdeveloped and directed forward [38,40]. In AMS, ears are often significantly reduced in size and low-set. Additionally, they may have an altered shape, folding, and fused earlobes [10,33].

Hair

Generalized excessive hairiness is not characteristic of AMS. Only in a few cases has excessive facial hair been observed [40]. Indeed, this is an important feature that helps differentiate BSS from AMS [2]. After birth, many patients with AMS lack lanugo, and sparse or absent hair on the scalp is often observed [10]. As patients with AMS age, their hair typically remains sparse and thin. Cases of absent hair in the pubic and axillary regions have been reported in adult patients [37].

Skin

A common symptom in patients with AMS is redundant skin, especially located on the hands, buttocks, feet, neck, and around the ears. Other abnormalities include excessive dryness, laxity, and prominent blood vessels in the skin. Early wrinkles and numerous furrows may be observed, making patients appear older than they actually are. Excess skin folds have been described between the eyebrows and in other parts of the face, extending towards the nose and mouth. Additionally, excessive skin pigmentation has been observed on the ears, neck, back, chest, and large pigmented patches on the arms [35,37,39]. Skin biopsies have been performed several times. In some cases, a decrease in the number of elastic fibers was observed, while in others, there were no specific changes, and collagen studies were normal [39].

Mammae

In adult female patients with AMS, the absence or underdevelopment of mammary glands may be observed. The nipples are usually small, and complete absence, supernumerary nipples, or wide nipple spacing may also occur [5,35].

Reproductive organs

In most cases, the genitalia of patients of both sexes were described as ambiguous. Abnormalities include the presence of a micropenis, which may be located posteriorly in the perineal area, cryptorchidism, poorly developed scrotum resembling labia majora, and absence of the scrotum [1,42]. In one patient, despite ambiguous genitalia detected at birth, normal menstruation occurred later in life. The same authors described a case where the urethral opening was located in the vaginal wall, along with the presence of underdeveloped labia majora. Additionally, one male patient was raised as female [35].

Other

In a 37-year-old patient with a confirmed *TWIST2* gene mutation, tracheal stenosis was observed. This is the first case of its kind, and it is uncertain whether it is directly related to AMS [41]. Several patients have been described with syndactyly and camptodactyly of the fingers, occurring bilaterally. Additionally, in one case, there was syndactyly of the toes [35]. AMS is typically not associated with intellectual disability, although a few patients have been noted to have a lower level of intellectual development [11,37,40].

Differential diagnosis

AMS and BSS share numerous facial and physical characteristics due to heterozygous mutations in the *TWIST2* gene, making differential diagnosis challenging. Both syndromes present with excessive facial creases, hypertelorism, and a wide mouth, among other features. However, AMS often exhibits more severe underdevelopment of the anterior eyelids and sparse scalp hair, while BSS is marked by generalized hypertrichosis and a greater tendency for hyperlax and atrophic skin. Additionally, AMS patients may have more pronounced genital anomalies and partial syndactyly of fingers. In contrast, Setleis syndrome, another disorder caused by *TWIST2* mutations, can be differentiated by its distinctive bitemporal narrowing with localized skin atrophy and the presence of entropion. Despite these distinguishing features, the considerable phenotypic overlap among AMS, BSS, and Setleis syndrome suggests they may form a spectrum of anomalies, rather than entirely separate entities [2].

Diagnostics

The clinical presentation may resemble other genetic syndromes, including BSS and SS, so making a diagnosis solely based on it can sometimes be difficult. However, suspicion of AMS typically arises shortly after birth, based on the analysis of the typical phenotype [42]. Family history is also helpful, as AMS is most likely inherited in an autosomal dominant manner [9,10].

However, to confirm the diagnosis, genetic testing should be performed [11,42]. Real-time PCR can be used to test the *TWIST2* gene for mutations [22]. Imaging studies can also be helpful in evaluating patients suspected of having AMS. Computer tomography or X-rays of the head may reveal underdeveloped zygomatic bones [5]. Some authors speculate that in the

future, AMS, BSS, and SS may be classified as a spectrum of anomalies [2]. The diagnostic process and subsequent therapy should be carried out by a multidisciplinary team of specialists, including geneticists, pediatricians, neonatologists, ophthalmologists, and urologists [4].

Treatment

AMS is a highly rare genetic disorder for which there is no specific therapy that could completely cure the disease. However, there are various forms of support for patients, such as surgical interventions and symptomatic treatment, which can help alleviate symptoms and improve the quality of life for those affected [43].

Treatment interventions and support for individuals with AMS should be adapted to the specific needs of the patient and determined collaboratively by specialists in agreement with the patient's family. In the care process of patients with AMS, it is particularly important, even essential, to establish an interdisciplinary team consisting of specialists from various fields, including pediatrics, genetics, plastic surgery, pediatric dentistry, otolaryngology, dermatology, maxillofacial surgery, ophthalmology, orthopedics, cardiology, and psychology [36]. Only through this multidisciplinary collaboration is it possible to comprehensively assess and treat patients with AMS, tailored to their individual health needs.

Plastic surgery – protecting the cornea and ensuring proper vision

The absence of eyelids, which is a component feature of this syndrome, can lead to the development of dry eye syndrome and corneal damage, which isa serious complication. This results directly from the lack of mechanical protection, exposing the eye to external

environmental factors such as wind, dust, and other irritants, posing the risk of worsening vision or even complete loss of sight [35].

To reduce ophthalmic complications such as corneal clouding, especially in newborns, and preserve visual function, corrective and reconstructive surgeries play a crucial role. In cases of severe eyelid eversion (ectropion) and underdevelopment, skin grafts may be used to improve eyelid closure. However, a potential side effect of this procedure may be difficulty in fully closing the eyes (lagophthalmos). Later in life, additional surgical procedures may be performed to further improve function and appearance. Simultaneously, early implementation of supportive therapy, such as moisturizing eye drops, can provide relief for symptoms of dry eye syndrome [44].

Due to the rarity of this syndrome and the necessity to create an individualized treatment plan tailored to the patient's needs, research continues to seek effective methods for preserving visual function. The method employed by Hollanders et al. in the treatment of AMS involved the use of masquerading flaps to protect the cornea and enable bilateral light entry into the eyes [42]. In the case described by the researchers of a premature infant with a severe AMS phenotype, intensive moisturizing eye therapy was initially applied. However, despite this, the boy developed serious traumatic keratopathy in the first few days after birth. As a result, for the next 6 weeks, the child's eyes were closed using masquerading flaps. In the second stage, at an adjusted age of 3 weeks, the flaps were partially incised, allowing for normal visual development while maintaining corneal protection. The conclusions drawn from this case confirm the effectiveness of the masquerade flaps method in preventing corneal damage and enabling proper visual development in patients with severe AMS phenotypes [42].

Plastic surgery – craniofacial anomalies, facial dysmorphia, and other developmental defects

Surgical treatment of patients with craniofacial anomalies, such as macrostomia, requires balancing multiple factors. Early interventions may be demanded by patients and their families, aiming to achieve the most natural facial appearance at a young age. However, performing radical surgeries during adolescence or early adulthood may lead to serious consequences for skull and craniofacial growth and negatively impact long-term functional and aesthetic outcomes. Therefore, a multidisciplinary approach involving an experienced team is crucial for determining the optimal timing and personalized treatment plan for each patient. To date, only case reports have been published, often containing limited information on the exact surgical procedures aimed at achieving a more natural facial appearance. There is also a lack of long-term monitoring of patients with AMS, making it difficult to develop clear guidelines on this issue. Corrective surgical procedures include facelifts, local repositioning, fat grafting, forehead lifts, Botox injections, orthognathic surgeries, and nose reconstruction with rib cartilage grafts [35,37] According to De Maria et al., these procedures may pose a greater risk in younger individuals because their bodies are still developing [2]. Therefore, it is important to postpone such significant procedures until the completion of skull and craniofacial growth to avoid the risk of disrupting their natural development [2]. In cases of necessity, corrective surgeries for developmental abnormalities of the ears, genital organs, or fingers can also be performed [43].

Symptomatic treatment

Symptomatic treatment used in AMS is a crucial aspect of patient care aimed at improving comfort and quality of life.

Aggressive eye moisturization is of utmost importance as patients often experience issues related to dry eye syndrome due to the characteristic features of this condition, such as underdeveloped eyelids. To ensure eye comfort and health, regular use of artificial tears, eye drops, and moisturizing ointments is necessary, along with the use of bubble protectors to prevent excessive drying of the eye surface and minimize the risk of infection. Regular consultations with an ophthalmologist are also crucial to monitor the eye's health status and adjust moisturizing therapy to the patient's individual needs [45].

Proper skincare also plays a significant role in AMS management, as patients may be prone to various dermatological issues such as dryness, roughness, or skin irritation. Regular use of emollients and oils can help maintain adequate moisture and prevent skin dryness. Additionally, it is important to avoid irritating factors and use soothing creams in case of irritation or inflammation [36]. Coordinating the skincare strategy should be entrusted to an experienced dermatologist who can adapt it to the individual needs and skin condition of each patient.

Psychological and social support

Psychological and social support is a crucial aspect of caring for patients with AMS and their families. Access to support groups, psychological consultations, and patient organizations can significantly help in coping with the challenges associated with AMS and provide essential emotional and informational support. Patient advocacy organizations actively contribute to raising public awareness about the condition and serve as a significant driving force for research aimed at improving the quality of life for affected individuals [46]. Psychosocial support also plays a significant role in the development process of AMS patients, who must confront societal pressure related to their physical appearance. Therefore, it is essential for an experienced

healthcare team to provide support both medically and psychosocially. It is also important for patients to have access to child psychologists throughout the treatment process, which can significantly aid in their adaptation and coping with emotional difficulties associated with the illness. Despite the challenges posed by AMS, patients note that they are aware that this condition primarily affects their external appearance and does not impact their physical or intellectual abilities, nor their ability to pursue their ambitions. Building self-worth and continuous support from family members are crucial for them [43].

Genetic testing and counseling

Genetic testing can help identify genetic mutations associated with AMS and enable assessment of the risk of inheriting the disease within the family. Genetic counseling can be beneficial for individuals with AMS and their families in understanding the disease, family planning, and making decisions regarding childcare [10,47,48].

Prognosis in AMS

The prognosis for individuals with AMS can vary and depends on many factors, including the severity of symptoms and the presence of additional congenital abnormalities. Because AMS is a rare genetic disorder, there is limited data on long-term prognosis. Additionally, due to the diversity of clinical presentation, each case of AMS requires individual assessment and therapeutic approach. Early diagnosis, appropriate medical care, and social support can help improve the quality of life for patients with this rare syndrome.

In some cases, AMS symptoms may be mild, and satisfactory functioning and quality of life can be achieved with proper medical care. Although individuals affected by the syndrome

may not drastically alter their appearance to meet societal standards, their life expectancy is not different from the average [3].

In other cases, when additional congenital defects or health complications are present, the prognosis may be more complicated [33].

Conclusions

Despite the concerning clinical presentation raising concerns about the newborn's survival, AMS is a condition that does not preclude a long life. However, such a distinct deviation from the norm in appearance may cause significant distress and anxiety, negatively impacting the patient's mental well-being and consequently, reducing their quality of life. Moreover, the diagnosis of a rare disease, not commonly seen in society, intensifies feelings of social isolation. Additionally, the medical community often focuses on physical and pathophysiological aspects, overlooking psychosocial issues. Paying attention to the mental well-being of AMS patients facilitates self-acceptance and enables taking a step towards destigmatizing individuals with a different appearance.

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