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Barbara Rybus-Kalinowska[1,2], Mariusz Kalinowski[3], Beata Łabuz-Roszak[1], Brygida Adamek[1], Bogumiła Wójcik-Niklewska[4], Jakub Warakomski[5], Lidia Hyla-Klekot[2]

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Impaired tear secretion as the first symptom of triple A syndrome in two siblings

Zaburzenia wydzielania łez jako pierwszy objaw zespołu Allgrove'a u dwojga rodzeństwa

[1] Department of Basic Medical Sciences, School of Public Health in Bytom, Medical University of Silesia in Katowice, Bytom, Poland
[2] Paediatrics and Oncology Centre in Chorzów, City Hospitals of Chorzów, Chorzów, Poland
[3] Department of Cardiac, Vascular and Endovascular Surgery and Transplantology, School of Medicine in Zabrze, Medical University of Silesia in Katowice, Zabrze, Poland
[4] Department of Ophthalmology with Paediatric Unit, Medical University of Silesia in Katowice, Katowice, Poland
[5] Department of Pathophysiology and Endocrinology, Faculty of Medicine in Zabrze, Medical University of Silesia, Katowice, Poland
Correspondence: Barbara Rybus-Kalinowska, MD, PhD, Department of Basic Medical Sciences, School of Public Health in Bytom, Medical University of Silesia, Piekarska 18, 41-902 Bytom, Poland, tel.: +48 32 397 65 45, fax: +48 32 397 65 37, e-mail: markal13@gmail.com

Abstract

Triple A syndrome is a rare, autosomal recessive disease. It is characterised by a triad of symptoms: alacrima, adrenocortical insufficiency and oesophageal achalasia. Atrophy of the optic nerve and a number of neurological disorders also occur in patients with this syndrome. Only about one hundred cases have been described in the literature since the first description by Allgrove in 1978. This paper presents a case report of siblings diagnosed with triple A syndrome. A 6-year-old girl developed adrenocortical insufficiency, axonal-demyelinating polyneuropathy and oesophageal achalasia, while her 3-year-old brother showed an abnormal adrenal reserve. Both children presented with the lack of tears during crying.

Keywords: triple A syndrome, child, dry eye

Streszczenie

Zespół Allgrove'a jest rzadko występującym, uwarunkowanym genetycznie zespołem chorobowym, dziedziczonym autosomalnie recesywnie. Charakteryzuje się triadą objawów: alakrimią, niewydolnością kory nadnerczy i achalazją przełyku. U pacjentów z tym schorzeniem opisano również zanik nerwu wzrokowego oraz szereg zaburzeń neurologicznych. Od pierwszego opisu Allgrove'a w 1978 roku w literaturze przedstawiono około 100 przypadków tego zespołu. W niniejszej pracy omówiono przypadek rodzeństwa, u którego rozpoznano zespół Allgrove'a. U 6-letniej dziewczynki wystąpiły niewydolność kory nadnerczy, polineuropatia aksonalno-demielinizacyjna oraz achalazja przełyku, natomiast u 3-letniego brata wykazano nieprawidłową rezerwę nadnerczową. U obojga dzieci występowało zjawisko braku łez podczas płaczu.

Słowa kluczowe: zespół Allgrove'a, dziecko, suche oko

INTRODUCTION

Triple A syndrome (or AAA syndrome, also known as achalasia-addisonianism-alacrima syndrome) is a condition characterised by the coexistence of alacrima (abnormal or absent tear production), oesophageal achalasia and an atypical presentation of primary adrenocortical insufficiency. The symptoms develop as a result of an autosomal recessive mutation in the *AAAS* gene on chromosome 12 (12q13). The estimated prevalence is 1 per 1,000,000 inhabitants per year. Symptoms usually develop in early childhood. Although most patients develop the whole triad, only two of the symptoms may occur (not always at the same time) in some patients[1]. Alacrima is usually the first noticeable symptom; however, some patients may be asymptomatic[2].

CASE REPORT

A 6-year-old girl and her 3-year-old brother were reported to an ophthalmology clinic due to the lack of tears during crying. This symptom drew attention during the girl's stay in a paediatric unit due to severe ketotic hypoglycemia. Diagnostic tests revealed primary adrenocortical insufficiency and axonal-demyelinating polyneuropathy. An abnormal adrenal reserve (currently without clinical manifestation) was found in her brother. Both children were put on oral hydrocortisone. The whole clinical picture raised a suspicion of triple A syndrome. Molecular diagnosis of the *AAAS* coding sequence revealed p.Ser263Pro mutation, confirming the initial diagnosis. Both children presented with a homozygous mutation, whereas both of their parents were confirmed as asymptomatic carriers of pathogenic p.Ser263Pro mutation.

The children reported no complaints during ophthalmological examination, which showed normal distance visual acuity: the right eye and the left eye: 1.0. During the assessment of the anterior segment, tear film break up time (TBUT) was evaluated and was less than 5 seconds. Schirmer's test was not performed due to lack of patient cooperation. Evaluation of the anterior segment revealed no abnormalities other than interrupted tear meniscus of less than 1 mm. The fundus of the right and the left eye was normal. Optical coherence tomography (OCT) of the optic nerve was performed in the girl, showing minor atrophy of nerve fibres in both right and left eye. Based on the examination, dry eye was diagnosed in both children, and treatment in the form of moisturising eye drops was initiated. After a few months, the children reported to the ophthalmology clinic for a routine check-up. Another hospitalisation of the girl took place before the check-up visit – this time due to dysphagia. Diagnostic tests confirmed oesophageal achalasia. Thus, the patient manifested the full triad of triple A syndrome symptoms. The siblings remain under the care of ophthalmology, neurology, gastroenterology and endocrinology clinics.

DISCUSSION

In 1978, Allgrove for the first time described two pairs of siblings with adrenal insufficiency, oesophageal achalasia and alacrima. The triad of these symptoms is known as the triple A syndrome or the AAA syndrome (also known as the Allgrove syndrome)[1]. Although the disease is usually diagnosed before the age of 10 years, many cases of triple A syndrome diagnosed in adult individuals have been described. The configuration and severity of the symptoms vary in frequency; only two of the three symptoms develop in some cases. So far, only about 100 cases of triple A syndrome have been reported globally. In 1996, Weber et al. localised the gene responsible for the symptoms of the AAA syndrome on 12q13[3]. The gene encodes ALADIN protein, which is involved in redox homeostasis in human adrenal cells and inhibits steroidogenesis. The mutation results in the substitution of serine for proline at position 263 of the amino acid chain in the protein and, consequently, the loss of its function[4].

Impaired tear production is one of the key symptoms of triple A syndrome. The symptoms associated with abnormal tear film formation are much less common in the paediatric population compared to adults. Data on the prevalence of dry eye syndrome in children under 18 years of age are sparse[5]. Dry eye syndrome may develop in children with Sjögren's syndrome, graft versus host disease, juvenile rheumatoid arthritis, familial dysarthria, diabetes, Stevens–Johnson syndrome, or triple A syndrome. Other causes of dry eye in children include the use of systemic antihistamines or retinoids[6]. Since impaired tear production is one of the key symptoms of triple A syndrome, it is important to evaluate the tear film and the protective eye apparatus during an ophthalmic examination. The diagnosis of dry eye syndrome in children poses difficulty due to the lack of full cooperation during the examination. Children may often be unable to clearly define their symptoms. The test uses a slit lamp consisting of a high-intensity light source and a biomicroscope to ensure magnification (6–40×). The use of Schirmer's test, which allows for the assessment of the aqueous component of the tear film, is rarely possible in children. Schirmer's test uses a paper strip inserted into the eye for about 5 minutes to measure the amount of moisture absorbed by the paper. The results are interpreted as follows: >15 mm wetting of the paper is considered normal result, 10–15 mm of moisture indicates mild tear deficit, 5–10 mm points to moderate deficit, and <5 mm is considered advanced dry eye syndrome. However, the test is less precise compared to tear film break-up time test as it allows for the evaluation of only one component of tear film (the aqueous layer), without the possibility to assess the moisture of the eye surface. Therefore, the test may be positive in some patients with dry eye syndrome. The tear biofilm may be also assessed based on the evaluation of tear meniscus – the normal meniscus should be >1 mm in height and have

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a convex shape. The tear meniscus is reduced and interrupted in patients with abnormal tear film. The tear film break-up time test is a non-invasive method to assess the tear film. It measures the time elapsed between a blink and tear film break-up. The test allows for the evaluation of the lipid layer of the tear film. It is usually performed with the use of a small amount of dye (fluorescein), which is introduced in the form of a drop or placed on a thin paper strip in the conjunctival sac. Break-up time shorter than 5 seconds indicates impaired eye moisturising with tear film instability due to impaired lipid layer of the tear film[7]. Alacrima, which may develop already in early childhood, is considered to represent the earliest symptom of triple A syndrome. This is the most consistent feature of this disease. Affected children produce very little or no tears when crying. In the description of clinical cases of triple A syndrome, histopathological evaluation of lacrimal glands showed a reduced number of secreting cells[2], while signs of lacrimal gland atrophy are seen in magnetic resonance imaging[8]. Mild alacrima is treated with local moisturising agents, while immunosuppressants (cyclosporine) are used for severe dry eye syndrome. In cases of resistance to local treatment, closure of lacrimal points may be performed[7].

Adrenocortical insufficiency usually manifests in the first decade of life. It is the main cause of death in patients with triple A syndrome. It may manifest with episodes of hypoglycaemia, hypertension and progressive skin hyperpigmentation. Currently, there is no treatment protocol for patients diagnosed with triple A syndrome who do not present with adrenocortical insufficiency. However, close monitoring of serum electrolytes, especially during episodes of acute diseases, should be introduced to avoid adrenal crisis. Hydrocortisone is the treatment of choice[9].

Oesophageal achalasia is very rare in the paediatric population, with a prevalence of less than 5% among children under the age of 15 years. It affects about 75% of patients with triple A syndrome and may be the first manifestation of the disease. Oesophageal achalasia usually manifests as vomiting, dysphagia, weight loss and chronic cough. It may cause difficulty eating and hypoglycaemia. These patients are often misdiagnosed with gastroesophageal reflux disease. Oesophageal achalasia requires surgical intervention. Patients presenting with this disorder require monitoring due to the risk of respiratory complications[10,11].

Furthermore, about 60% of patients with triple A syndrome develop nervous system disorders in the form of peripheral neuropathy, pyramidal symptoms, autonomic dysfunction, ataxia, dementia and parkinsonism. Neurological disorders occur at a later time than the other triad components and increase with age[12]. Due to the risk of optic nerve atrophy, periodic visual field test, optical coherence tomography of the optic nerve, and, especially in small children, electrophysiological examination (visually evoked potentials) should be performed in patients with triple A syndrome[13].

CONCLUSIONS

Triple A syndrome, which may manifest clinically at any time in life and with various symptom configurations, requires multidisciplinary diagnosis and treatment. The prevalence, which is 1 per 1,000,000 inhabitants per year, may be underestimated due to misdiagnosis or late diagnosis. Since alacrima is a rare symptom, impaired tear secretion combined with gastrointestinal symptoms and endocrine disorders in children should raise concerns and lead to extended diagnosis including molecular testing for triple A syndrome to avoid potentially fatal consequences. Due to the autosomal recessive inheritance of the disease, the probability of having a sick child by parents both of whom are carriers of the mutated gene is 25%. Genetic findings are the basis for offering prenatal diagnosis for couples with further reproductive plans[14]. Patients with triple A syndrome require regular ophthalmological, endocrinological, gastroenterological and neurological follow-up.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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