Case report / *Prikaz primera*

Triple A syndrome - case report

Trojni A sindrom - prikaz primera

Eva Supovec[1], Nataša Smrekar[2], Eva Mislej*[2]
[1]*Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia*
[2]*Department of Gastroenterology, University Medical Centre Ljubljana, Ljubljana, Slovenia*
Slovenian Journal of Gastroenterology / Gastroenterolog 2024; 1: 95–98

***Keywords**: Triple-A syndrome, Allgrove syndrome, achalasia, dysphagia, adrenal insufficiency*

***Ključne besede**: Trojni A sindrom, Allgrove sindrom, ahalazija, disfagija, insuficienca nadledvičnice*

ABSTRACT

The Triple-A or Allgrove syndrome (MIM*231550) is an autosomal-recessive multisystem disorder, characterised by the triad of achalasia, alacrima (reduced or absent tearing), and adrenocorticotropic hormone (ACTH)-resistant adrenal insufficiency. It is a rare condition; its exact prevalence is not yet to be known. We present the case of a 33-year-old woman with a history of triple A syndrome with associated Addison's disease and alacrima who was admitted to our clinic because of dysphagia.

IZVLEČEK

Triple A sindrom (MIM*231550) je avtosomno-recesivna multisistemska motnja, za katero je značilna triada ahalazije, alakrime (zmanjšano ali odsotno solzenje) in insuficience nadledvične žleze. Je redko stanje, njegova natančna prevalenca še ni znana. Predstavljamo primer 33-letne ženske z anamnezo sindroma trojnega A s pridruženo Addisonovo boleznijo in alakrimo, ki je bila sprejeta na našo kliniko zaradi disfagije.

INTRODUCTION

The Triple-A or Allgrove syndrome (MIM*231550) is an autosomal-recessive multisystem disorder characterised by the triad of achalasia, alacrima (reduced or absent tearing), and adrenocorticotropic hormone (ACTH)-resistant adrenal insufficiency. It is a rare condition, first described by Allgrove et al. in 1978 (1). Since then, over a hundred case reports have been published, however, its exact prevalence is yet to be known (2). The syndrome results from the mutations in the AAAS (achalasia–addisonianism–alacrima syndrome) gene on chromosome 12q13, which encodes a 546-amino acid nuclear envelope protein called *ALADIN* (alacrima, achalasia, adrenal insufficiency, neurologic disorder), which belongs to the WD-repeat family of proteins (3–8). A classic patient is a healthy born baby with the congenital absence of tear production, who develops adrenal insufficiency in the first decade of life and achalasia later on, usually in the first or second decade of life (9, 10). In this case report, we present a 33-year-old woman previously

*Eva Mislej, MD
Department of Gastroenterology, University Medical Centre Ljubljana, Japljeva ulica 2, 1000 Ljubljana, Slovenia
E-mail: eva.mislej@kclj.si

Received: 3/27/2024; Review: 4/20/2024; Accepted for publication: 5/3/2024

diagnosed with Triple A syndrome with known Addison's disease and alacrima. The patient was admitted to our clinic with a chief complaint of a month-long dysphagia. Subsequently, she was diagnosed with achalasia of cardia which presented in her fourth decade of life for the first time.

CASE REPORT

A 33-year-old woman with a history of triple A syndrome with associated Addison's disease and alacrima was admitted to our clinic because of dysphagia. Over the past month, the patient experienced dysphagia to solid foods but was able to ingest liquids. In the last seven days, she has been experiencing vomiting after meals. Additionally, she reported chest pains, dry cough, weakness and chills. She has unintentionally lost 7 kg in the past month. Her family history was negative. She had a history of numerous miscarriages. Her only gastroscopy was performed at the age of 17, during which time the oesophagus was slightly narrowed, but achalasia was not confirmed. She has never undergone oesophageal manometry or X-ray of the oesophagus until now. On examination, her height was 150 cm and her weight was 50 kg. Her blood pressure was 102/67 mmHg. Her skin and mucosa were pale. Lungs were clear on auscultation except for muted breathing at the base of the right posterior pulmonary lobe. The remaining physical exam was unremarkable. Her baseline blood work examination revealed hypokalaemia (3,7 mmol/L), high CRP levels (134 mg/L) and high procalcitonin (5,20 μg/L). Gastroscopy, performed at admission, showed the typical appearance of achalasia with a severely distended oesophagus, filled with liquid food. Computed tomography of the chest also demonstrated a distended (up to 5cm), fluid-filled oesophagus associated with achalasia as well as centrilobular nodules with a milk-glass appearance in the right upper and middle pulmonary lobe - most likely an aspiration pneumonia because of severe vomiting; and moderate right-sided pleural effusion. The patient received parenteral support with a gradual increase in caloric intake due to severe malnutrition according to GLIM criteria. Because of aspiration pneumonia, she underwent a seven-day therapy with amoxicillin with clavulanic acid. Therapy with hydrocortisone, which she had already been receiving before admission, was increased. Oesophageal manometry showed increased integrated relaxation pressure (48mmHg) without peristalsis and panesophageal pressurization, thus confirming the diagnosis of type 2 achalasia.

Heller's myotomy will be performed as a definitive treatment.

DISCUSSION

Our patient presented with all three of the cardinal features defining the Allgrove syndrome – namely alacrima, adrenal insufficiency and achalasia of the cardia. Although Triple-A syndrome is classically described as a triad of named features, phenotypic heterogeneity is significant even within the same family. Therefore, diagnosis of the triple-A syndrome is often a challenge. Since there is no specific genetic-phenotypic correlation patients with the same mutation can have different phenotypes (4, 9, 10). Alacrima is usually the earliest and the most consistent sign of the disease (10–14). It is commonly present since infancy but most often remains unrecognized (10, 11, 13, 15). Left untreated, it may lead to keratopathy and corneal ulceration (9, 16–19). Other ophthalmic features consistent with the diagnosis of triple-A syndrome include lacrimal gland atrophy that can be seen on neuroimaging (16, 17, 20); pupillary abnormalities, including sluggish pupils, tonic pupils, and hypersensitivity to dilute miotics; and optic atrophy (16). The diagnosis of alacrima is confirmed by Schirmer's test and is managed by artificial tears and topical lubricants (18). Adrenal insufficiency is not congenital but develops gradually. It most commonly manifests in the first decade of life (10, 13, 14), but may develop as late as in the third decade (13, 14). It can result in sudden death due to severe hypoglycaemic episodes (21, 22). Other symptoms of adrenal failure include recurrent vomiting, hyperpigmentation of the skin and mucous membranes and developmental delays (10, 21, 23). While most patients have isolated glucocorticoid deficiency (14, 23), mineralo-

corticoid deficiency has also been reported (6, 10, 11, 13, 24). The standard 250 μg ACTH stimulation test proves the diagnosis of adrenal insufficiency. If negative, an insulin-induced hypoglycaemia test should be performed (25). Therapy includes lifelong glucocorticoid replacement therapy with hydrocortisone and fludrocortisone in the case of absent mineralocorticoid production (26). Achalasia of the cardia is frequently the initial symptom for seeking medical help (11). It is caused by aberrant peristalsis and insufficient relaxation of the lower oesophageal sphincter (27). Symptoms include dysphagia to solids and liquids, regurgitation, weight loss and/or failure to thrive (18, 23, 28), chest pain (14) as well as recurrent or chronic pulmonary disease as a result of aspiration, especially in infants and toddlers (9). Signs of dysphagia and regurgitation may be present for years until the diagnosis of achalasia is established, with patients often being misdiagnosed and treated for gastroesophageal reflux (29). In our patient, the inability to consume food due to persistent dysphagia and vomiting resulted in inadequate dietary intake, causing weight loss and malnutrition, even though her BMI was still within the normal range (22.22 kg/cm^2). Namely, a study showed that achalasia patients are at nutritional risk regardless of the presenting weight category (30). Malnutrition was also a possible cause of frequent miscarriages the patient experienced. Even though achalasia was confirmed only in the fourth decade of her life, the patient had likely experienced difficulty swallowing long before but adapted her eating patterns to her symptoms. She had not sought medical attention up until this point, with delayed seeking of medical attention being the norm in patients with dysphagia (31). Rapid treatment was necessary as she already had complications, namely aspiration pneumonia. Diagnosis of achalasia can be made with barium oesophagograms or with manometry (9), which shows oesophageal dysmotility, usually characterised by both aperistalsis and a hypertonic lower oesophageal sphincter (14). The latter was also true for our patient. Treatment may include Heller's or endoscopic myotomy, pneumatic balloon dilatation, or botulinum toxic injections (9–11, 18, 32). Besides the classic triad, other variable features of the Triple A syndrome have been reported including dermatological abnormalities such as palmoplantar hyperkeratosis (13, 33); short stature (10, 13, 21, 24, 34), microcephaly (10), osteoporosis (35), delayed wound healing and dysmorphic features (11, 14). Commonly, patients can also exhibit signs of progressive neurological disorders, which are most often autonomic but can also be central or peripheral, leading some authors to use the term 4A syndrome (achalasia, alacrima, adrenal insufficiency, and autonomic and other neurologic abnormalities) (9, 10, 13, 36). Signs of autonomic dysfunction include orthostatic hypotension, arrhythmias, absent or reduced sweating, pupillary abnormalities, accommodative spasm, etc. Other neurological abnormalities include mental retardation or developmental delay, hyperreflexia, muscle weakness, ataxia, dysarthria, bulbospinal amyotrophy, optical atrophy, etc (10–13, 15, 21, 34–38).

CONCLUSION

Even though Allgrove syndrome is a rare entity, it must be considered in the differential diagnosis of achalasia, especially when either alacrima or adrenal insufficiency or even neurological abnormalities are present. A mutation analysis of the AAAS gene should be performed to confirm the diagnosis. For those patients with an established diagnosis of 3A, we recommend routine inquiry of symptoms that may be related to achalasia and prompt referral to gastroenterology and surgical specialities when indicated. The disease cannot be cured; but can be managed by symptomatic therapy.

References

1. Allgrove J, Clayden GS, Grant DB, Macaulay JC. Familial glucocorticoid deficiency with achalasia of the cardia and deficient tear production. Lancet Lond Engl. 1978 Jun 17;1(8077):1284–6.
2. Manoria P. Triple A syndrome: a case report. Trop Doct. 2021 Apr 1;51(2):263–5.
3. Handschug K, Sperling S, Yoon SJ, Hennig S, Clark AJ, Huebner A. Triple A syndrome is caused by mutations in AAAS, a new WD-repeat protein gene. Hum Mol Genet. 2001 Feb 1;10(3):283–90.
4. Houlden H, Smith S, de Carvalho M, Blake J, Mathias C, Wood NW, et al. Clinical and genetic characterisation of families with triple A (Allgrove) syndrome. Brain. 2002 Dec 1;125(12):2681–90.
5. Tullio-Pelet A, Salomon R, Hadj-Rabia S, Mugnier C, de Laet MH, Chaouachi B, et al. Mutant WD-repeat protein in triple-A syndrome. Nat Genet. 2000 Nov;26(3):332–5.
6. Sandrini F, Farmakidis C, Kirschner LS, Wu SM, Tullio-Pelet A, Lyonnet S, et al. Spectrum of mutations of the AAAS gene in Allgrove syndrome: lack of mutations in six kindreds with isolated resistance to corticotropin. J Clin Endocrinol Metab. 2001 Nov; 86(11):5433–7.
7. Huebner A, Kaindl AM, Braun R, Handschug K. New insights into the molecular basis of the triple A syndrome. Endocr Res. 2002 Nov;28(4):733–9.
8. Cronshaw JM, Matunis MJ. The nuclear pore complex protein ALADIN is mislocalized in triple A syndrome. Proc Natl Acad Sci U S A. 2003 May 13;100(10):5823–7.
9. Sarathi V, Shah NS. Triple-A syndrome. Adv Exp Med Biol. 2010;685:1–8.
10. Brooks BP, Kleta R, Stuart C, Tuchman M, Jeong A, Stergiopoulos SG, et al. Genotypic heterogeneity and clinical phenotype in triple A syndrome: a review of the NIH experience 2000-2005. Clin Genet. 2005 Sep;68(3):215–21.
11. Grant DB, Barnes ND, Dumic M, Ginalska-Malinowska M, Milla PJ, von Petrykowski W, et al. Neurological and adrenal dysfunction in the adrenal insufficiency/alacrima/achalasia (3A) syndrome. Arch Dis Child. 1993 Jun;68(6):779–82.
12. Prpic I, Huebner A, Persic M, Handschug K, Pavletic M. Triple A syndrome: genotype-phenotype assessment. Clin Genet. 2003 May; 63(5):415–7.
13. Gazarian M, Cowell CT, Bonney M, Grigor WG. The '4A' syndrome: adrenocortical insufficiency associated with achalasia, alacrima, autonomic and other neurological abnormalities. Eur J Pediatr. 1995 Jan;154(1):18–23.
14. Moore PS, Couch RM, Perry YS, Shuckett EP, Winter JS. Allgrove syndrome: an autosomal recessive syndrome of ACTH insensitivity, achalasia and alacrima. Clin Endocrinol (Oxf). 1991 Feb;34(2): 107–14.
15. Pombo M, Devesa J, Taborda A, Iglesias M, García-Moreno F, Gaudiero GJ, et al. Glucocorticoid deficiency with achalasia of the cardia and lack of lacrimation. Clin Endocrinol (Oxf). 1985 Sep;23(3):237–43.
16. Brooks BP, Kleta R, Caruso RC, Stuart C, Ludlow J, Stratakis CA. Triple-A syndrome with prominent ophthalmic features and a novel mutation in the AAAS gene: a case report. BMC Ophthalmol. 2004 Jun 24;4:7.
17. Mullaney PB, Weatherhead R, Millar L, Ayyash II, Ayberk H, Cai F, et al. Keratoconjunctivitis sicca associated with achalasia of the cardia, adrenocortical insufficiency, and lacrimal gland degeneration: Keratoconjunctivitis sicca secondary to lacrimal gland degeneration may parallel degenerative changes in esophageal and adrenocortical function. Ophthalmology. 1998 Apr;105(4):643–50.
18. Ambrosino MM, Genieser NB, Bangaru BS, Sklar C, Becker MH. The syndrome of achalasia of the esophagus, ACTH insensitivity and alacrima. Pediatr Radiol. 1986;16(4):328–9.
19. Babu K, Murthy KR, Babu N, Ramesh S. Triple A syndrome with ophthalmic manifestations in two siblings. Indian J Ophthalmol. 2007 Aug;55(4):304.
20. Tsilou E, Stratakis CA, Rubin BI, Hay BN, Patronas N, Kaiser-Kupfer MI. Ophthalmic manifestations of Allgrove syndrome: report of a case. Clin Dysmorphol. 2001 Jul;10(3):231–3.
21. Dumić M, Radica A, Jušić A, Stefanović N, Murko Z. Selective ACTH insensitivity associated with autonomic nervous system disorders and sensory polyneuropathy. Eur J Pediatr. 1987 Nov 1;146(6):592–4.
22. Clark AJL, Weber A. Adrenocorticotropin Insensitivity Syndromes. Endocr Rev. 1998 Dec 1;19(6):828–43.
23. Geffner ME, Lippe BM, Kaplan SA, Berquist WE, Bateman JB, Paterno VI, et al. Selective ACTH insensitivity, achalasia, and alacrima: a multisystem disorder presenting in childhood. Pediatr Res. 1983 Jul;17(7):532–6.
24. Lanes R, Plotnick LP, Bynum TE, Lee PA, Casella JF, Fox CE, et al. Glucocorticoid and partial mineralocorticoid deficiency associated with achalasia. J Clin Endocrinol Metab. 1980 Feb;50(2):268–70.
25. Salehi M, Houlden H, Sheikh A, Poretsky L. The diagnosis of adrenal insufficiency in a patient with Allgrove syndrome and a novel mutation in the ALADIN gene. Metabolism. 2005 Feb; 54(2):200–5.
26. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016 Feb;101(2):364–89.
27. Vaezi MF, Pandolfino JE, Yadlapati RH, Greer KB, Kavitt RT. ACG Clinical Guidelines: Diagnosis and Management of Achalasia. Am J Gastroenterol. 2020 Sep;115(9):1393–411.
28. Ghoshal UC, Thakur PK, Misra A. Frequency and factors associated with malnutrition among patients with achalasia and effect of pneumatic dilation. JGH Open Open Access J Gastroenterol Hepatol. 2019 May 14;3(6):468–73.
29. Flokas ME, Tomani M, Agdere L, Brown B. Triple A syndrome (Allgrove syndrome): improving outcomes with a multidisciplinary approach. Pediatric Health Med Ther. 2019 Aug; 29 (10):99-106.
30. Newberry C, Vajravelu RK, Pickett-Blakely O, Falk G, Yang YX, Lynch KL. Achalasia Patients Are at Nutritional Risk Regardless of Presenting Weight Category. Dig Dis Sci. 2018 May;63(5):1243–9.
31. Wilkins T, Gillies RA, Thomas AM, Wagner PJ. The prevalence of dysphagia in primary care patients: a HamesNet Research Network study. J Am Board Fam Med JABFM. 2007;20(2):144–50.
32. Thomas RJ, Sen S, Zachariah N, Chacko J, Mammen KE. Achalasia cardia in infancy and childhood: an Indian experience. J R Coll Surg Edinb. 1998 Apr;43(2):103–4.
33. Counahan R, West R. Ocular and fingertip abnormalities in isolated glucocorticoid deficiency. J Pediatr. 1974 Oct;85(4):580–1.
34. Ehrich E, Aranoff G, Johnson WG. Familial achalasia associated with adrenocortical insufficiency, alacrima, and neurological abnormalities. Am J Med Genet. 1987 Mar;26(3):637–44.
35. Dumić M, Radica A, Sabol Z, Plavsić V, Brkljacić L, Sarnavka V, et al. Adrenocorticotropic hormone insensitivity associated with autonomic nervous system disorders. Eur J Pediatr. 1991 Aug;150(10): 696–9.
36. Goizet C, Catargi B, Tison F, Tullio-Pelet A, Hadj-Rabia S, Pujol F, et al. Progressive bulbospinal amyotrophy in triple A syndrome with AAAS gene mutation. Neurology. 2002 Mar 26;58(6):962–5.
37. Makari G, Hoffman WH, Carroll JE, Savage DR, Van der Zalm T. Autonomic dysfunction and adrenocortical unresponsiveness to ACTH. J Child Neurol. 1988 Jul;3(3):174–6.
38. Dumars KW, Williams JJ, Steele-Sandlin C. Achalasia and microcephaly. Am J Med Genet. 1980;6(4):309–14.