Case Reports in Ophthalmology

Case Rep Ophthalmol 2023;14:288–294
DOI: 10.1159/000531131
Received: December 6, 2022
Accepted: May 14, 2023
Published online: July 7, 2023

Case Report

A Case of Autism Spectrum Disorder with Perforated Keratomalacia due to Vitamin A Deficiency

Daisuke Nakata[a, b] Sayaka Kakehi[a] Hiroshi Okada[a] Koji Hirano[b, c]
Masayuki Horiguchi[b] Yasuki Ito[b]

[a]Department of Ophthalmology, Toyokawa City Hospital, Toyokawa, Japan; [b]Department of Ophthalmology, Fujita Health University School of Medicine, Toyoake, Japan; [c]Department of Ophthalmology, Toyota Memorial Hospital, Toyota, Japan

Keywords
Vitamin A deficiency · Autism spectrum disorder · Keratomalacia · Corneal perforation · Smartphone

Abstract
We report a case of a patient with autism spectrum disorder (ASD) and perforated keratomalacia secondary to vitamin A deficiency. A 6-year-old boy complained of difficulty in opening the eyelids. The ocular conjunctiva was hyperemic and keratinized with purulent ocular (eye) discharge. Both corneas showed epithelial defects with hypopyon. The serum vitamin A level was ≤5 IU/dL (normal 97–316), leading to a diagnosis of xerophthalmia and keratomalacia due to vitamin A deficiency. Intramuscular injection of vitamin A (50,000 IU/day), as well as oral administration of multivitamin (containing 2,500 IU of vitamin A) and zinc supplement at 50 mg/day, allowed him to open both eyes and show interest in tablet devices 14 days after the diagnosis. During the course of the treatment, corneal perforation was observed, but it was closed without contact lens wear or amniotic patch and managed with vitamin A replacement therapy and antimicrobial eye drops. The epithelium extended to the area of the right cornea that had been melted, and although scarring corneal opacity remained, there were no obvious signs of infection. Early diagnosis is difficult because children with ASD do not express complaints, and vitamin A deficiency should be considered in patients with a severely unbalanced diet and complaints of difficulty opening the eyelids.

Correspondence to:
Daisuke Nakata, dnakata@fujita-hu.ac.jp

Case Rep Ophthalmol 2023;14:288–294
DOI: 10.1159/000531131

Introduction

Vitamin A deficiency is classified as primary when owing to malnutrition [1, 2] or secondary when resulting from liver dysfunction [1, 3] or gastrointestinal surgery [1, 4]. Ophthalmologic complications associated with vitamin A deficiency include night blindness and xerophthalmia [5, 6]. In developing countries, where people are prone to insufficient vitamin A intake, the primary form of the deficiency is predominant in infants and has remained a major cause of childhood blindness over the last decades [2]. In contrast, in developed countries with better dietary habits, the primary form is rare, thus the predominant form is the secondary, due to underlying diseases such as liver disorders or gastrointestinal surgery [3, 4].

In this study, we report a case of primary vitamin A deficiency caused by an unbalanced diet associated with autism spectrum disorder (ASD), leading to xerophthalmia and keratomalacia. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/00053131).

Case Report

A 6-year-old boy was admitted to our department with fever of unknown origin and complained of difficulty in opening both eyelids. Fever higher than 38°C persisted for 2 weeks. He was diagnosed with dry eye by a local ophthalmologist, who prescribed a sodium hyaluronate ophthalmic solution for follow-up observation. As the fever persisted, the child was admitted to the pediatric department of Toyokawa City Hospital for examination and treatment. His past history included ASD diagnosed at 3 years of age and multiple hospitalizations for urinary tract infections. He communicated in written form only due to ASD, and he was a prolific tablet device user. He had an unbalanced diet, which consisted of white rice, French fries, and snacks. He had a history of self-injurious behavior, which involved putting his index finger into his mouth and rubbing the eyes with it. The patient's mother was undergoing treatment for depression.

On admission, his height was 107.0 cm, significantly lower than the Japanese average (116.7 cm), and his weight was 14.5 kg, lower than the average weight of 6-year-old children (mean 21.4 kg). The body mass index was 12.66, and he was very skinny. His temperature was 38.2°C, there was no obvious lymphadenopathy or skin rash, and blood tests showed an elevated inflammatory response with a white blood cell count of 29,900/mm^3 (normal 3,300–8,600) and a C-reactive protein level of 4.95 mg/dL (normal 0.00–0.14). Urinalysis revealed increased numbers of white blood cells (2+) and presence of bacteria (3+), with *Enterococci* and *E. coli*, in the urine culture. Considering the recurrence of the urinary tract infection, intravenous ampicillin (250 mg/kg) treatment was started, but the fever did not resolve. He was referred to the ophthalmology department the day after admission to investigate the cause of difficulty in opening the eyelids together with the fever of unknown origin.

Visual acuity and intraocular pressure could not be measured because of ASD-related symptoms. Because he was unable to cooperate with slit-lamp microscopy, a portable slit-lamp microscope was used at the bedside for examination. Both ocular conjunctivae were hyperemic, keratinized, and had folds associated with xerophthalmia, with purulent ocular discharge. The cornea showed extensive epithelial defects measuring 9 × 7 mm in the right eye and 7 × 5 mm in the left eye, and edematous opacity with hypopyon (Fig. 1). The vitreous body and fundus were not visible. Findings were recorded using a smartphone (iPhone 8, Apple Inc., CA, USA) with the consent of the family. Photography was performed as previously reported [7], and the anterior segment of the eye was photographed using the video mode of the smartphone camera application and saved as a still image.

Case Rep Ophthalmol 2023;14:288–294
DOI: 10.1159/000531131

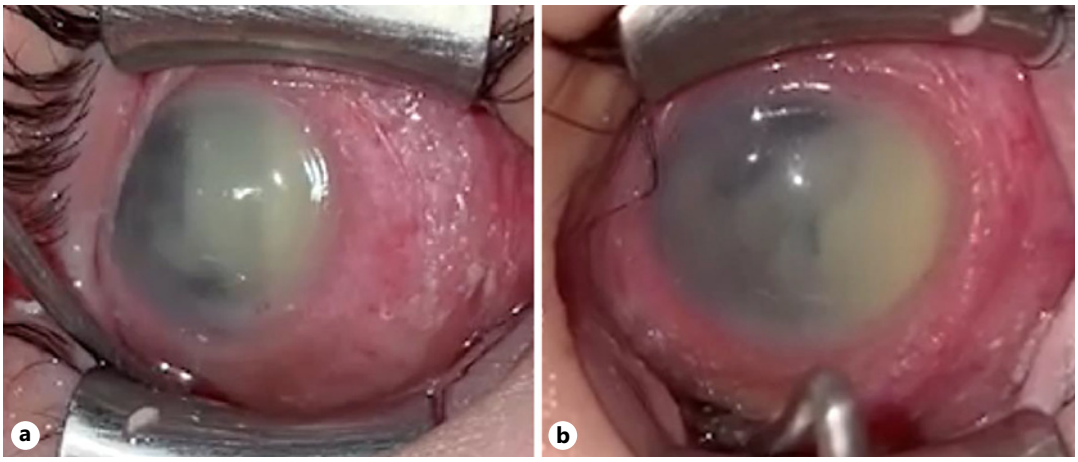

Fig. 1. Anterior segment findings at initial examination imaged using a smartphone. **a** Right eye. **b** Left eye. Both ocular conjunctivae were hyperemic and had folds associated with xerophthalmia. Cornea showed extensive epithelial defects and edematous opacity with hypopyon. The patient had been in the lateral position until just before examination; the abscess was seen on the left side of the eye.

He was diagnosed with infected corneal ulcers in both eyes, and the initial treatment consisted of both moxifloxacin hydrochloride and cefmenoxime hydrochloride ophthalmic solutions six times a day, together with sodium hyaluronate ophthalmic solution four times a day. Since *Staphylococcus aureus* was identified in the ocular lipid culture, the pediatric antibiotic was replaced with intravenous cefepime hydrochloride (1 g/kg). The hypopyon showed a decreasing trend, but the corneal epithelial defects did not improve. On day 7, a corneal perforation was observed in the right eye, the iris was incarcerated, and a shallow anterior chamber was observed.

Based on his health history and clinical findings, we suspected vitamin A deficiency and performed additional blood tests, which revealed markedly decreased levels of serum vitamin A (≤5 IU/dL, normal 97–316), zinc (28 μg/dL, normal >80), and retinol-binding protein (0.6 mg/dL, normal 3–6). A diagnosis of xerophthalmia and keratomalacia due to vitamin A deficiency was reached.

Oral administration of multivitamin (containing 2,500 IU of vitamin A) at 1 g/day was initiated as a vitamin A supplement, and Noveldin®, a zinc acetate preparation, was initiated as a zinc supplement at 50 mg/day. For treating the corneal perforation, vitamin A replacement therapy and antibacterial eye drops were continued because wearing contact lens was not possible due to ASD. On the seventh day of treatment, serum vitamin A levels improved to 125 IU/dL, but due to a lack of improvement in corneal and conjunctival characteristics, the patient was switched to intramuscular injection of vitamin A (50,000 IU/day). On day 14, anterior chamber formation was obtained without the need for amniotic membrane filling and closure; the patient was able to open both eyelids and showed interest in tablet devices. He was treated with sodium hyaluronate eye drops, and vitamin A was administered in oral form as multivitamin supplementation. Blood tests showed serum vitamin A and zinc levels had improved to 215 IU/dL and 97 μg/dL, respectively, and the patient was discharged from the hospital after approximately 1 month.

After discharge from the hospital, the patient's unbalanced diet did not improve although he continued to take multivitamins. Three months after discharge from the hospital, he attended elementary school and operated a tablet device without any problem, although he showed difficulties on the vision screening. Blood tests showed serum vitamin A levels at

Case Rep Ophthalmol 2023;14:288–294
DOI: 10.1159/000531131

157 IU/dL and serum zinc levels at 159 μg/dL, which remained within normal limits. Slit-lamp microscopy revealed slightly hyperemic but well-moistened conjunctiva. Transparency of the corneal parenchyma in the left eye was achieved, but the area of melting in the right eye remained as a cicatricial corneal opacity with epithelialization; there were no obvious signs of infection (Fig. 2).

Discussion

The patient presented to the ophthalmologist with a chief complaint of difficulty in opening the eyelids. A clinical history of ASD, together with vitamin A and zinc deficiencies resulting from several years of poor nutrition due to an unbalanced diet, led to xerophthalmia and keratomalacia, as well as an infected corneal ulcer due to self-injurious behavior. As a result, he was unable to open his eyelids due to pain.

Vitamin A is a fat-soluble vitamin found in animal products such as meat, fish, and eggs, as well as in plant foods such as carrots and spinach; thus, it can be obtained through the diet [1, 5]. Vitamin A plays an important role in the maintenance of visual function, and is a key factor in rhodopsin production. Vitamin A also plays a role in the normal differentiation of the corneal and conjunctival epithelium and in the promotion of goblet cell differentiation. Night blindness is one of the first symptoms of vitamin A deficiency [5]. In advanced stages, necrosis of the corneal stroma leads to keratomalacia [6]. According to the World Health Organization (WHO), 190 million people, or one-third of the world's preschool children, showed vitamin A deficiencies in 2009 [1]. However, in developed countries, vitamin A deficiency due to insufficient intake is rare, and instead, secondary vitamin A deficiency due to malabsorption after gastrointestinal surgery has been reported in many cases [1, 4]. In the field of urology, vitamin A supplementation has also been reported to stabilize the urothelium and prevent recurrent lower urinary tract infections in children [8], which suggests that its deficiency may be involved in recurrent tract infections. Considering the clinical history of the patient, it is possible to speculate that vitamin A deficiency may have been involved in his previous recurrent urinary tract infections.

Vitamin A deficiency does not cause xerophthalmia in the early stages of the disease. Instead, it is usually detected based on night blindness associated with retinal light sensitivity changes [6]. Further, white spots from the posterior pole to the periphery of the fundus, loss of rod signals in the electroretinogram (ERG) [9], irregularity of the ellipsoid zone, and loss of interdigitation zone on optical coherence tomography (OCT) [10] have been reported. However, in patients with communication disorders such as the present case, xerophthalmia and keratomalacia may be diagnosed suddenly without previous complaints of night blindness; tests such as OCT and electroretinogram are difficult to take. Thus, vitamin A deficiency may be overlooked, especially in children with ASD because of difficulties in communication and examination [11, 12].

Retinol-binding protein is a specific transport protein for blood retinol. Zinc is required for its synthesis, and it has been reported that many cases of vitamin A deficiency are accompanied by zinc deficiency [13]. Serum zinc levels were also low in the present case. Zinc is a trace element necessary for the activation of more than 300 enzymes, and it plays an important role in cell division and nucleic acid metabolism. The physiological effects of zinc are diverse and involve skin metabolism, immune function, and taste. It is also involved in height growth and skeletal development in children [13]. Zinc deficiency causes growth retardation, taste disorders, delayed wound healing, and susceptibility to infection, suggesting a role in short stature and recurrent urinary tract infections.

Case Rep Ophthalmol 2023;14:288–294
DOI: 10.1159/000531131

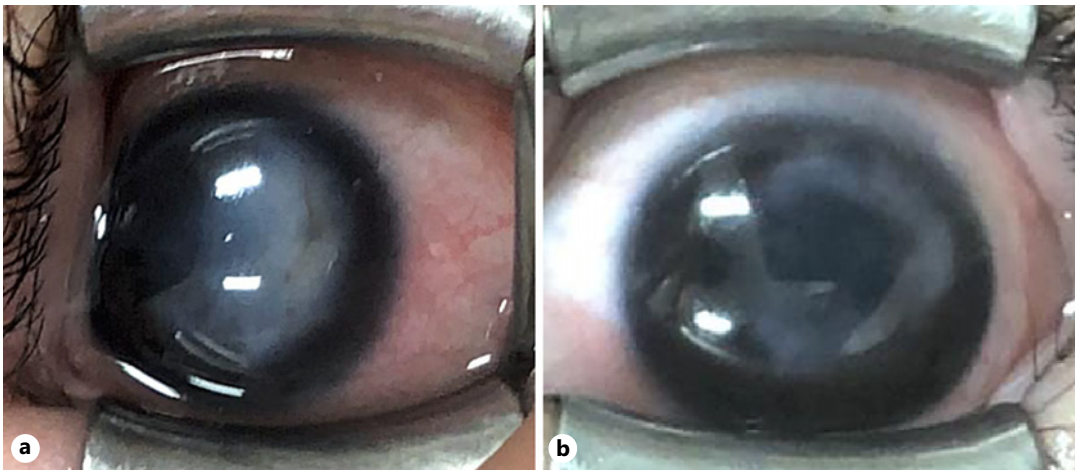

Fig. 2. Anterior segment findings 3 months after initial examination imaged using a smartphone. **a** Right eye. **b** Left eye. Both eyes had slightly hyperemic conjunctiva but were well moistened. Transparency of the corneal parenchyma in the left eye was achieved, but the area of melting in the right eye remained as a cicatricial corneal opacity with epithelialization.

ASD comprises a complex set of developmental disorders characterized by impairments in communication, social interaction, and repetitive behaviors. Impairments in sensory processing are extremely common. The prevalence of ASD is increasing and is currently estimated to affect 1 in 150 children. Children with ASD are known to have increased rates of selective diets with decreased fruit, dairy, vegetable, and protein intake [14]. Children with ASD have significantly more feeding problems and eat a significantly less variety of foods, which results in a higher risk of developing nutritional deficiencies due to an unbalanced diet. In addition, due to their behavioral impairments, they are less likely to cooperate with medical examinations and treatment, which may delay diagnosis and treatment of the disease thus aggravating it [11, 12]. In the present case, the patient had a predilection for carbohydrates, especially French fries. Behaviors attributed to developmental disabilities, such as difficulty communicating, lack of subjective symptoms, and refusal to see the doctor, may also have contributed to the development of the corneal disorder, due to lack of early consultation. Early treatment is critical, as it contributes to preventing irreversible changes and to maintain visual function. With this aim, collaboration among pediatricians, nutritionists, staff at disability welfare facilities, and other professionals is highly relevant.

In this case, the vitamin A intake might have been extremely reduced due to a long-term unbalanced diet, leading to vitamin A deficiency. Although it is difficult to determine whether the cause of corneal ulcer was infectious or noninfectious, a decrease in the barrier function of the cornea in keratomalacia due to vitamin A deficiency might have occurred, and hypopyon occurred concomitantly with bacterial infection ulcers such as *Staphylococcus aureus*. As the degree of corneal perforation was minimal, only vitamin A replacement therapy and antibacterial eye drops were used to repair the corneal perforation and the corneal findings improved dramatically. Contact lens wear and amniotic membrane transplantation were not performed due to the patient's self-injurious behavior, which was considered difficult to manage postoperatively. Corneal findings may provide clues to the detection of this disease.

The actual number of patients with this condition may be higher because people with unbalanced diets and eating disorders do not consult an ophthalmologist until an abnormality appears in the keratoconjunctiva. In particular, in the case of an unbalanced diet with ASD in the background, there is no complaint until ocular pain occurs, so it is considered that a considerable number are latent.

Table 1. Reported cases of vitamin A deficiency in Japan, a developed country (Hirano et al. [15])

Factor of vitamin A deficiency	Number of patients
Digestive disorders	17
Dialysis	7
Eating disorder	3
Unbalanced diet	7
Inherited hypo-retinol-binding proteinemia	1
Undernutrition	0

Hirano et al. [15] summarized the background factors of vitamin A deficiency cases with ocular complications in Japan, a developed country, in international and domestic journals (Table 1). The most reported factors so far are not undernutrition but digestive disorders including gastrointestinal and hepatic disorders, followed by an unbalanced diet, along with hemo- and peritoneal dialysis. However, most patients with digestive disorder or dialysis present to the ophthalmologist with night blindness as the main complaint, whereas those with unbalanced diet or eating disorder do not present to the ophthalmologist until abnormalities in the cornea appear; therefore, the case number may be underestimated.

For corneal transplantation, penetrating keratoplasty or lamellar keratoplasty is necessary for perforated corneas because iridencleisis into the Descemet's membrane has not been assessed by anterior segment OCT or ultrasound biomicroscopy. However, penetrating keratoplasty or lamellar keratoplasty is not recommended because of difficulties in postoperative management due to the patient's self-injurious behavior and maternal depression. Prevention of amblyopia in the right eye appears to be the immediate concern.

Examination of infants with ASD is relatively difficult in daily practice, and the recording of anterior segment findings is largely based on medical records, which depend on the examining physician. In order to standardize the examination of the anterior segment, photographing it should be useful for monitoring changes over time and implementing any required immediate action. The recording and publication of smartphone images were approved by the Clinical Research Committee of Toyokawa City Hospital, along with the consent of the family.

In conclusion, we encountered a case of a boy with ASD who developed keratomalacia due to vitamin A deficiency caused by a severely unbalanced diet. Vitamin A deficiency should be considered in patients with a severely unbalanced diet and complaints of difficulty opening the eyelids. It is difficult for the Department of Ophthalmology to provide guidance to address Vitamin A deficiency, and the patient should be referred to the Department of Pediatrics or the Department of Dietetics. However, as in this case, it is desirable to have a system that allows collaboration with these departments, as corneal findings can be the initial indication of this disease.

Acknowledgments

We would like to thank Editage (www.editage.com) for the English language editing.

Statement of Ethics

This case report was conducted in accordance with the World Medical Association Declaration of Helsinki. The Ethics Committee of Toyokawa City Hospital reviewed the study protocol and waived the need for approval. Written informed consent was obtained from the parents of the patient for the publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors declare that they did not receive any funding for this study.

Author Contributions

Daisuke Nakata, Sayaka Kakehi, and Hiroshi Okada examined the patients and collected clinical data. Daisuke Nakata drafted the manuscript. Koji Hirano edited the manuscript. Masayuki Horiguchi and Yasuki Ito have reviewed the manuscript. All authors have read and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 World Health Organization. Global prevalence of vitamin A deficiency in populations at risk 1995–2005. WHO global database on vitamin à deficiency. Geneva: World Health Organization; 2009.
2 Humphrey JH, West KP Jr, Sommer A. Vitamin A deficiency and attributable mortality among under-5-year-olds. Bull World Health Organ. 1992;70(2):225–32.
3 Saeed A, Dullaart RPF, Schreuder TCMA, Blokzijl H, Faber KN. Disturbed vitamin A metabolism in non-alcoholic fatty liver disease (NAFLD). Nutrients. 2017 Dec 29;10(1):29.
4 Lee WB, Hamilton SM, Harris JP, Schwab IR. Ocular complications of hypovitaminosis a after bariatric surgery. Ophthalmology. 2005 Jun;112(6):1031–4.
5 Smith J, Steinemann TL. Vitamin A deficiency and the eye. Int Ophthalmol Clin. 2000 fall;40(4):83–91.
6 Sommer A. Xerophthalmia, keratomalacia and nutritional blindness. Int Ophthalmol. 1990 May;14(3):195–9.
7 Lord RK, Shah VA, San Filippo AN, Krishna R. Novel uses of smartphones in ophthalmology. Ophthalmology. 2010 Jun;117(6):1274–e3.
8 Yilmaz A, Bahat E, Yilmaz GG, Hasanoglu A, Akman S, Guven AG. Adjuvant effect of vitamin A on recurrent lower urinary tract infections. Pediatr Int. 2007 Jun;49(3):310–3.
9 Genead MA, Fishman GA, Lindeman M. Fundus white spots and acquired night blindness due to vitamin A deficiency. Doc Ophthalmol. 2009 Dec;119(3):229–33.
10 Berkenstock MK, Castoro CJ, Carey AR. Outer retina changes on optical coherence tomography in vitamin A deficiency. Int J Retina Vitreous. 2020 Jun 5;6(23):23.
11 Adachi S, Torio M, Okuzono S, Motomura Y, Ichimiya Y, Sonoda Y, et al. Vitamin A deficiency-associated corneal perforation in a boy with autism spectrum disorder: a case report and literature review. Nutrition. 2021 Oct;90:111275.
12 Chan E, Buzzard J, Helms R, Grigorian AP. Evaluation and clinical course of keratomalacia with descemetocele in a child with autism and vitamin A deficiency. J Pediatr Ophthalmol Strabismus. 2020 Jan 24;57(6):e1–3.
13 Christian P, West KP. Interactions between zinc and vitamin A: an update. Am J Clin Nutr. 1998;68(2 Suppl):435S–41S.
14 Cermak SA, Curtin C, Bandini LG. Food selectivity and sensory sensitivity in children with autism spectrum disorders. J Am Diet Assoc. 2010 Feb;110(2):238–46.
15 Hirano K, Tanaka H, Iwami M. Xerophthalmia caused by psychic-induced vitamin A deficiency. Ophthalmol Writ Jpn. 2019;61(7):763–9.