Vitamin A Deficiency Due to Selective Eating as a Cause of Blindness in a High-Income Setting

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Vitamin A is a fat-soluble micronutrient involved in the regulation of several physiologic functions, such as visual acuity, epithelial tissue integrity, immune response, and gene expression, thus playing a crucial role in childhood growth and development. Although vitamin A deficiency (VAD) in resource-limited settings is still an actual issue and represents the leading cause of preventable childhood blindness, its occurrence in high-income countries is rare, although possibly underdiagnosed because of its nonspecific early manifestations. A good awareness of VAD symptoms and risk factors could aid its early diagnosis, which is fundamental to undertake a prompt treatment and to prevent ocular complications. Nevertheless, the role of restrictive dietary habits, increasingly common in developed countries, is often overlooked in infants and children. We present a case of VAD with permanent ocular sequelae in a 5-year-old girl from a high-income country. In the case described, VAD ensued from a highly restricted diet, mainly limited to oat milk, which had been followed for more than 2 years. This child presented with ocular symptoms, opportunistic infection, anemia, poor growth, and a diffuse squamous metaplasia of the bladder; after commencing retinol supplementation, a gradual healing of clinical VAD manifestations occurred, with the exception of the ocular sequelae, which resulted in irreversible visual loss.

Vitamin A is a fat-soluble vitamin involved in crucial physiologic processes, including organogenesis, tissue differentiation, visual function, and immune response,[1] thus playing a key role in growth and development during childhood.

In resource-limited settings, vitamin A deficiency (VAD) is mainly due to chronic malnutrition and is estimated to affect up to 50% of preschool-aged children[2]; in this population, VAD represents the leading cause of preventable blindness[3] and is associated with increased rates of morbidity and mortality.[4] On the other hand, in high-income countries, childhood VAD is thought to be rare and primarily related to underlying medical conditions (eg, malabsorption, liver diseases[5]), whereas other possible risk factors, such as adherence to selective diets for either sociocultural, environmental, or health reasons,[6] are rarely taken into account.[7] Although an early diagnosis is fundamental to undertake a prompt retinol supplementation and to prevent permanent blindness, VAD can present a diagnostic challenge to pediatricians. Its early symptoms, such as xerophthalmia and hemeralopia, are subtle and nonspecific and are thus frequently overlooked.[3] Furthermore, the progressive impairment of multiple

abstract

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Drs Martini, Rizzello, and Romanin collected and reviewed the patient's data and wrote the first draft of the manuscript; Drs Bergamaschi, Corsini, and Grandi actively contributed in the clinical management of the patient and critically revised the manuscript; Dr Fiorentino performed the histological evaluation and critically revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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TABLE 1 Anthropometric Measures, Blood Tests, and Urinalysis Results During Hospital Stay and at Follow-up Evaluation

Time From Diagnosis, d	Admission	Diagnosis	Follow-up				Reference Values[a]
	−28	0	30	60	180	360	
Weight, kg (percentile)	14.5 (<3°)	15 (<3°)	15.5 (<3°)	17 (3–10°)	18 (10°)	22 (>25°)	
Height, cm (percentile)	105 (<3°)	105 (<3°)	105 (<3°)	105 (<3°)	106 (3°)	112 (3–10°)	
White blood cell count, n/mmc	22 200	12 480	6920	6460	10 010	6920	4200–9000
Neutrophils, %	74.3	44.4	31.7	36.6	27.5	30.2	40–74
Lymphocytes, %	20.5	46.1	57.6	53.7	61.8	58.2	19–48
Hemoglobin, g/dL	9.3	8.8	9.9	10.1	12.3	12.6	12–15
C-reactive protein, mg/dL	<0.03	0.3	<0.03	<0.03	<0.03	0.04	<0.8
Albumin, g/dL	2.6	2.9	4.3	4.5	4.2	4.4	3.5–5.5
Total cholesterol, mg/dL	63	58	108	159	195	—	<200
HDL, mg/dL	37	6	42	53	67	—	>45
LDL, mg/dL	17	26	60	—	—	—	<130
Iron, µg/dL	36	16	38	18	20	70	35–145
Ferritin, ng/mL	107	74	18	6	6	7	15–140
Vitamin A, mmol/L	—	1.1	1.4	1.3	1.7	1.4	1.1–2.3
RBP, mg/dL	—	3.5	4.8	—	—	—	3–6
Vitamin B_{12}, pg/mL	—	1406	1281	457	—	488	145–914
PT	1.24	1.25	1.15	1.11	1.07	1.09	<1.2
aPTT	0.89	0.85	1.06	1.04	1.01	1.09	0.82–1.25
Thyrotropin, mcIU/mL	—	52.1	1.4	1.5	1.54	1.14	0.27–4.2
FT3, pg/mL	—	2.4	6.4	5.6	4.3	5.6	2.2–5.5
FT4, pg/mL	—	6.3	14.7	15.6	17.5	15.7	9–17
Zinc, µmol/mL	—	18.9	—	—	—	—	9.8–16.8
Urinalysis	Leukocytes Bacteria Squamous cells	Leukocytes Bacteria Squamous cells	Normal	Normal	Normal	Normal	

aPTT, activated partial thromboplastin; FT3, free T3; FT4, free T4; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PT, prothrombin time; —, not applicable.
[a] Reference values used in our laboratory.

organ systems (sensory organs, endocrine and immune systems, bone marrow, skin, and mucosae) associated with the worsening of vitamin A status can be misdiagnosed as other more common pathologic conditions,[8] thus potentially contributing to delayed diagnosis and treatment.

We report a case of VAD with multisystem involvement in a high-income 5-year-old girl, caused by a persistent selective diet and ensuing in permanent visual loss.

CASE REPORT

This 5-year-old girl was admitted to the Pediatric Department of St. Orsola-Malpighi University Hospital (Bologna, Italy) with fever and severe keratoconjunctivitis. Photophobia and epiphora were reported to have first appeared 1 year before and to have gradually worsened to bilateral conjunctival injection and purulent discharge unresponsive to topical antibiotics.

At admission, the patient also presented with thin scalp hair, dystrophic skin covered with lanugo, and diffuse muscle atrophy. Blood tests revealed moderate anemia, hypoalbuminemia, and significantly low levels of total and low-density lipoprotein cholesterol (see Table 1), whereas the urinalysis revealed pyuria, bacteriuria, and abundant squamous cells. The girl's weight and height at admission were well below the third percentile for age; both birth weight and target height were above the 75th percentile, but other anthropometric data were not available.

From the time of admission, the patient showed irritability and feeding refusal, which the parents ascribed to her poor physical condition; because of the persistence of this behavior, parenteral nutrition (PN) was started on day 7 of hospitalization.

Combined antibiotic and antifungal eye drops were also administered, but no improvement in ocular symptoms occurred over the first week. Ultrasound biomicroscopy, performed on day 9, revealed right corneal thinning and left corneal perforation, requiring corneal patch graft repair.

A catheter urine culture, collected in view of persistent pyuria and bacteriuria, was positive for *Pseudomonas aeruginosa*; therefore, on day 6, treatment with ceftazidime was undertaken. In the following days, however, the urine turned progressively turbid and bladder ultrasound revealed a thickening of the bladder wall and gross, hyperechoic particles suspended within its lumen (Fig 1). Because urine cultures were persistently positive for *P aeruginosa*, after a 7-day course, ceftazidime was

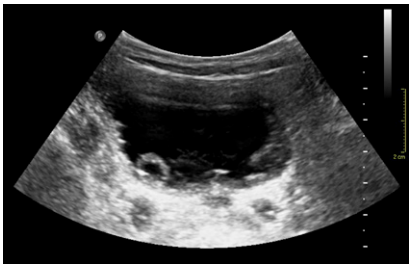

FIGURE 1
Bladder ultrasound evaluation showing thickening of the bladder wall and hyperechoic particles within the lumen.

changed to meropenem and teicoplanin. On day 20, while still on antibiotics, the patient flushed out in the urine a whitish tissue fragment, which on histologic examination was found to be entirely composed of acellular keratin material. A cystoscopy evaluation was thus performed on day 25, showing a diffuse white patch of bladder mucosa (Fig 2A); histology revealed squamous metaplasia of the urothelium with extensive hyperkeratinization (Fig 2B).

The combination of bladder metaplasia, ocular symptoms, and the opportunistic infection eventually led us to consider VAD. On day 28, serum vitamin A levels were thus determined as 1.1 mmol/L (PN ongoing for 21 days). Furthermore, serum levels of vitamin B_{12} were remarkably high, whereas zinc, iron, and ferritin fell within normal ranges (see Table 1). A significant elevation of thyrotropin (52.1 mcIU/mL) was also noticed, with evidence of an enlarged thyroid gland at neck ultrasound. In view of these findings, parenteral supplementation of vitamin A (retinol, 1000 μg/day) and oral levothyroxine (6.25 μg/day) were started.

The main causes of malabsorption (celiac disease, pancreatic insufficiency, intestinal bowel disease, intestinal infections, immunodeficiency) were investigated, yielding negative results. The patient's dietary habits were thus thoroughly reexamined

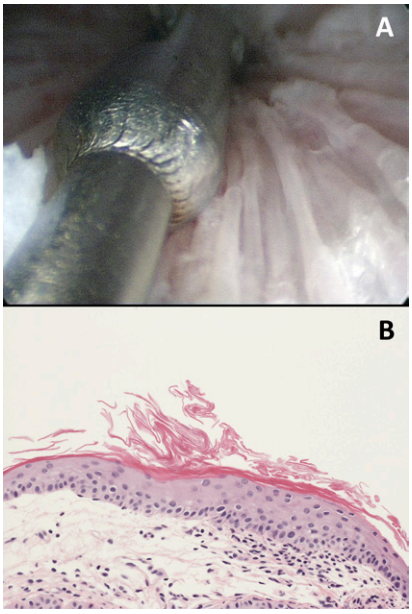

FIGURE 2
Squamous metaplasia of bladder mucosa. A, Cystoscopic appearance. B, Histologic evidence of metaplastic urothelium with extensive hyperkeratinization and shedding of acellular keratin material.

to chase possible overlooked information: a significantly restricted diet, consisting mainly of oat milk and ongoing for over 2 years, was eventually revealed by the parents. A psychosocial evaluation of the whole family was consequently performed, disclosing a conflictual mother-daughter relationship and an unsupportive family environment; therefore, both psychological and nutritional rehabilitation were undertaken.

In the following weeks, the patient improved, her urine gradually cleared, and urine culture results became negative. Under a dietician's guidance, she progressively adopted a varied and nutritionally balanced diet, which allowed PN to be discontinued 1 month after VAD diagnosis and an intravenous-to-oral switch of retinol administration (1500 μg/day). After a 3-month hospitalization, the patient was discharged in good condition and on oral retinol supplementation; at discharge, vitamin A serum levels had gradually increased, whereas vitamin B_{12} had returned to normal.

Anthropometric measurements and laboratory test results at follow-up evaluations are shown in Table 1. The patient continued on a varied diet, and serum retinol remained within the normal range. As thyroid function progressively normalized, substitutive therapy was discontinued after 9 months. Satisfactory catch-up growth gradually occurred; at the 2-year evaluation, height and weight had reached the 25th and 50th percentiles, respectively. Although most of the VAD-related clinical features completely recovered, a worsening of the ocular symptoms occurred despite retinol supplementation. The patient developed irreversible retinal atrophy in the left eye, whereas the right corneal thinning was complicated by a severe infection with ensuing phthisis bulbi, eventually resulting in permanent bilateral visual loss.

DISCUSSION

This case describes the occurrence of VAD resulting from a prolonged, strictly selective diet in a high-income child.

After oral intake, vitamin A is absorbed by enterocytes and metabolized into its predominant circulating form, retinol, which combines with its carrier, retinol-binding protein (RBP), and transthyretin.[9] By binding specific cell or nuclei receptors, the resulting complex regulates several functions, including visual acuity, epithelial tissue integrity, immune competence, and gene expression.[1] In the presence of VAD, or in the case of impaired RBP synthesis, these processes are inadequately supported and multiple clinical manifestation may develop, the most common being ocular symptoms, anemia, and increased susceptibility to infections.[10] These

findings were all present in the case described; additionally, squamous metaplasia of the bladder, a rare but characteristic condition ensuing from the VAD-related impairment of epithelial regeneration,[11,12] was observed. By reducing nocturnal growth hormone secretion, VAD can lead to significant growth restriction, usually responsive to vitamin A supplementation[13]; this is consistent with the significant catch-up growth observed in this patient after undertaking VAD treatment. Vitamin A is also known to influence the pituitary-thyroid axis[14]; although the high thyrotropin levels observed in this patient might be first ascribed to her poor clinical condition, a concomitant role for VAD could be hypothesized.

Serum retinol levels are frequently used to determine individual vitamin A status; current cutoff values defining VAD are 0.7 mmol/L,[15] whereas values <1.05 mmol/L identify subjects with a marginal status.[16] Although the clinical manifestations in the present case were suggestive of severe VAD, serum retinol was not significantly reduced; this finding might be explained by the fact that, at the time of measurement, PN had already been ongoing for 21 days, providing vitamin A intake equal to the recommended dietary allowance (400 μg/day[17]). Consistent with its homeostatic control mechanisms, however, serum retinol reflects vitamin A stores only when they are either extremely high or severely depleted[18]; hence, between these extremes, it may not reliably correlate with individual vitamin A status or clinical signs of deficiency. RBP has also been proposed as a surrogate for VAD assessment.[19] RBP, however, has a short half-life and previous studies on both animals[20] and malnourished children on PN[21] have shown that, soon after undertaking vitamin A supplementation, its serum levels rapidly increase. Hence, the normal RBP values observed in the present case are consistent with parenteral vitamin A administration, which at the time of measurement had been ongoing for 3 weeks.

In the case described, VAD ensued from a persistent selective diet, consisting mainly of oat milk. Storage processes for oat milk cause significant losses of vitamins A and B_{12}[22]; nevertheless, some of the main products currently available, such as the 1 the patient consumed, are fortified with the latter but not with the former.[23] These data are consistent with the high serum levels of vitamin B_{12} observed in the present case, which progressively normalized after oat milk discontinuation. The effects of this diet were further evidenced by the low cholesterol levels, consistent with the properties of oat β-glucan, which hampers the intestinal uptake of dietary cholesterol and enhances its hepatic conversion into bile acids.[24] Oat milk products are also among the nondairy plant-based milk substitutes with the lowest protein content[23]; the ensuing protein malnutrition, highlighted by the patient's hypoalbuminemia, may have contributed to worsen VAD symptoms by affecting liver synthesis of RBP,[25] which is crucial for retinol cellular intake.

To the best of our knowledge, this case is the first report of VAD with permanent sequelae resulting from severe selective eating in early childhood and reveals how restrictive dietary habits can place children at risk for VAD even in high-income settings.

The main sources of preformed vitamin A are animal liver, egg yolk, whole milk, and dairy products, whereas fruit and green leafy and yellow vegetables are rich in provitamin A carotenoids.[26] Hence, if VAD is suspected, the nutrition history should be carefully examined, with particular reference to the following dietary features: strict exclusion of meat, eggs, and dairy products, which is becoming increasingly common (eg, unbalanced vegan diets)[27]; the so-called cafeteria diet, increasingly popular in the modern society, which consists of energy-dense, low-quality food providing large amounts of carbohydrates and vegetable lipids[28]; extreme dietary protein restriction that, though rare in high-income countries, can result in functional VAD[25] by affecting RBP synthesis.

In the present case, the abnormal eating behavior was attributed to an impaired maternal relationship and family functioning, which are reported as the main psychosocial causes underlying selective eating in preschool-aged children.[29] Other conditions, such as multiple food allergies,[30,31] mental disorders,[32] and poor socioeconomic status[33] have also been associated with selective diets and ensuing micronutrient deficiencies and thus need to be investigated at the patient's history.

The case described provides a real example of how VAD can affect different systems and organs, thus resulting in a diagnostically challenging entity even in high-income settings, where diagnostic resources are easily accessible and available. To avoid permanent complications, the varied range of VAD clinical manifestations should be kept in mind not only by pediatricians but also by the subspecialty physicians potentially involved in the differential diagnosis; to this end, a multidisciplinary discussion of complex cases such as the 1 described soon after hospital admission may contribute to optimize and shorten the related diagnostic process.

CONCLUSIONS

A good awareness of VAD signs, symptoms, and risk factors is fundamental for early diagnosis

in infants and children from low-prevalence settings to prevent the establishment of ocular sequelae that can persist even after adequate vitamin A status is restored.

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ABBREVIATIONS

PN: parenteral nutrition
RBP: retinol-binding protein
VAD: vitamin A deficiency

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