American Journal of Ophthalmology Case Reports 29 (2023) 101781

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Dent disease presenting with nyctalopia and electroretinographic correlates of vitamin A deficiency

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ARTICLE INFO

Keywords:
Dent disease
Nyctalopia
Vitamin A deficiency
Retinol binding protein

ABSTRACT

Purpose: To report a unique case of Dent Disease presenting with nyctalopia associated with vitamin A deficiency and abnormal electroretinogram findings without prior systemic symptomatology.

Observations: A 16-year-old male presented with a several month history of nyctalopia and peripheral vision deficits. Central visual acuity, anterior and posterior segment examinations, and macular optical coherence tomography were unremarkable. Electroretinogram (ERG) testing revealed a rod-cone dystrophic pattern, with further workup demonstrating serum vitamin A deficiency (VAD). Laboratory evaluation revealed renal dysfunction and proteinuria with a significantly elevated urinary retinol-binding protein (RBP). Kidney biopsy showed glomerular and tubular disease.

Genetic screening for inherited renal disease was performed identifying a hemizygous pathogenic variant c.2152C>T (p.Arg718*) in the *Chloride Voltage-Gated Channel 5* (*CLCN5)* gene, confirming the diagnosis of X-linked Dent Disease. Following vitamin A supplementation, our patient reported resolution of nyctalopia and reversal of abnormal ERG findings were demonstrated.

Conclusions and Importance: To our knowledge, this is the first case in the literature describing Dent disease solely presenting with ophthalmic symptoms of nyctalopia and abnormal electroretinogram findings that later reversed with vitamin A repletion. This case stresses the importance for clinicians to consider renal tubular disorders in the differential for VAD.

1. Introduction

Vitamin A deficiency (VAD) is associated with ocular complications including xerosis, corneal ulceration, keratomalacia, and nyctalopia, with the latter typically manifesting as the first symptom of acquired VAD.[1–3] VAD is typically caused by poor nutritional intake, decreased intestinal absorption, or poor storage as seen in liver disease.[4,5] Once absorbed through the intestinal epithelium, approximately 95% of serum vitamin A is bound to retinol binding protein (RBP), enabling bloodstream transport to target tissues and to the liver for storage.[4,6] The interaction between serum RBP levels and serum retinol levels have been well-described, and RBP deficiency has been associated with ophthalmic disease linked to vitamin A deficiency.[6–8]

Urinary losses of RBP can result in RBP deficiency and clinical manifestations of VAD. Dent disease is an X-linked disorder characterized by low-molecular weight proteinuria, nephrocalcinosis, and progressive renal failure.[9,10] This renal tubular disorder typically presents with systemic findings of renal insufficiency, at an early age, prior to clinically symptomatic Vitamin A deficiency.[9,11,12] There have been reports of patients with known Dent disease who endorsed symptoms of recurrent nyctalopia that resolved upon vitamin A supplementation.[9,12] However, to our knowledge, there are no reports in the literature of nyctalopia presenting as the initial symptom of Dent disease.

Here, we present a case of nyctalopia as the first and only presenting symptom in a patient later diagnosed with Dent Disease. Furthermore, we demonstrate abnormal electroretinogram findings that have not yet

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https://doi.org/10.1016/j.ajoc.2022.101781
Received 21 May 2022; Received in revised form 24 November 2022; Accepted 12 December 2022
Available online 15 December 2022
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been previously reported in Dent disease that reversed with vitamin A supplementation.

2. Case description

A 16-year-old male, with no significant past medical or ocular history, was referred by his primary care physician due to a several month history of nyctalopia and peripheral vision loss in both eyes. Systemic review was negative for cardiac, pulmonary, neurologic, otologic, dermatologic, skeletal, renal and other symptoms or end-organ manifestations of inherited retinal diseases. Birth and developmental histories were unremarkable, the patient was of normal weight and height, and he endorsed a well-balanced diet. Review of available laboratory tests were unremarkable. Neither the patient nor the family reported any abnormal prior laboratory testing. Family history was unremarkable and parents denied consanguinity (Fig. 1).

On initial ophthalmologic examination, visual acuity was 20/20 bilaterally, and confrontational visual fields was full in both eyes. Intraocular pressure was 16 mmHg in the right eye and 13 mmHg in the left eye. Anterior segment examination was unremarkable, and dilated funduscopic examination was normal. Macular optical coherence tomography (OCT) and fundus autofluorescence were unremarkable (Supplementary Figs. 1 and 2). On full-field electroretinographic (ERG) testing according to ISCEV standards,[13] light-adapted responses demonstrated normal a- and b-waves, though a mild delay in peak response was noted on 30Hz flicker. Dark-adapted responses revealed borderline reduced a-wave responses to 0.01, 3.0, and 10.0 photopic units cd.s.m^2 stimuli demonstrated markedly attenuated b-wave responses (Fig. 2). These findings suggested a rod-cone dystrophic pattern of response.

A buccal swab was collected from the patient for next-generation sequencing and 330 genes were analyzed (Invitae, San Francisco, CA, USA) using a no-cost inherited retinal disease (IRD) testing as is standard in the IRD clinic at the University of California San Diego when IRDs are suspected. The patient was found to be heterozygous for a *TYR* missense variant c.1217C>T (p.Pro406Leu), previously reported to be associated with autosomal recessive oculocutaneous albinism.[14] However, given the lack of blonde hair, pale skin or a blonde fundus to suggest carrier status for TYR, it was concluded that this finding did not explain our patient's presentation.

As ocular examination was normal, serum vitamin A levels were obtained revealing moderate VAD with a level of 0.14mg/L (reference range 0.26–0.70mg/L). The patient was initiated on oral vitamin A supplementation at 2800μg/day, and his primary care physician was notified for further work-up of causes of vitamin A deficiency. Workup for VAD revealed an elevated serum creatinine at 1.2mg/dL (reference 0.6–1.0 mg/dL) estimated glomerular filtration rate 62 mL/min/1.73 m^2 by Schwartz 2 equation and 70 mL/min/1.73 m^2 by CKiD U25 estimating equation; review of previous records demonstrated similarly mildly elevated serum creatinine 18 months prior, though this value was not felt to be indicative of underlying renal pathology, since it was observed during an unrelated febrile illness, as may be often observed. Serum liver function tests, fecal fat measurements, cystic fibrosis sweat chloride screening, celiac screening, and serum levels of other fat-soluble vitamins were unremarkable. Urinalysis demonstrated nephrotic-range proteinuria (100 mg/dL) and microscopic hematuria. Renal ultrasound showed mildly echogenic kidneys suggestive of renal parenchymal disease and a 4 mm renal calculus in the left kidney.

The patient was referred to the pediatric nephrology service, and further investigations confirmed nephrotic range proteinuria (urine total protein/creatinine ratio 2.39 gm/gm (normal <0.2 gm/gm; urine microalbumin/creatinine ratio 357 mg/gm (normal <30 mg/gm)) and hypercalciuria (urine calcium/creatinine ratio 0.30 gm/gm (normal <0.21 gm/gm). Renal biopsy was performed revealing 42 glomeruli, of which 10 had total or near-total sclerosis, 3 had segmental sclerosis, and 5 with crescents (Fig. 3). In addition, interstitial fibrosis, tubular atrophy, and interstitial inflammation was noted, while no definitive immune deposits were identified. Thus, histopathology was reported as consistent with a "burned-out" glomerulonephritis, though later serologic workup for glomerulonephritis, including ANA, dsDNA, ASO, complements, ANCA, and hepatitis panel were normal.

Further investigation noted a high proportion of beta-2 microglobulin (197 mg/L, reference range <0.24mg/L) and elevated urinary RBP (>100,000 mcg/L, no established reference range in children), suggesting an underlying tubular disorder rather than a glomerular process. Serum retinol binding protein level was measured at 3.7 mg/dL (reference range 1.5–6.7mg/dL). This prompted next-generation sequencing analysis of 424 genes for renal tubular disorders, nephrotic syndrome, and focal segmental glomerulosclerosis (FSGS) (Invitae, San Francisco, CA, USA), which revealed a hemizygous pathogenic variant c.2152C>T (p.Arg718*) in the *Chloride Voltage-Gated Channel 5* (*CLCN5)* gene on the Xp11.22 locus. This confirmed a molecular diagnosis of X-linked Dent disease. Further investigations were performed to exclude disease associated with Dent disease.

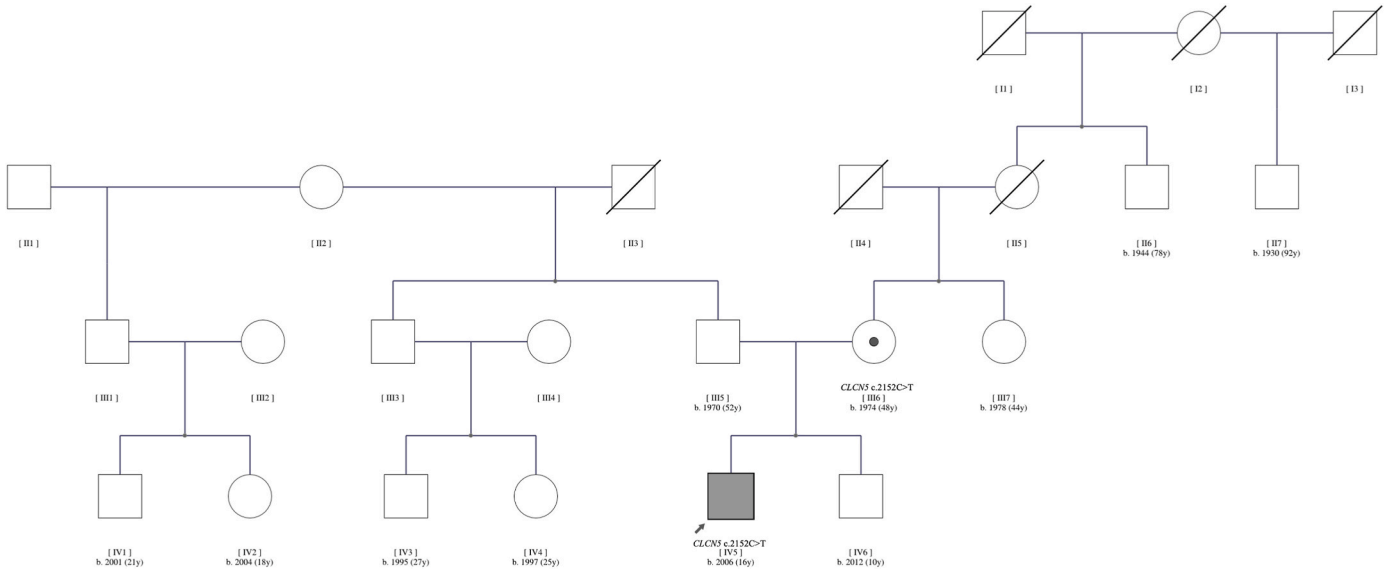

Fig. 1. *Four generation family pedigree.* Patient IV5 is the proband, patient III6 is the carrier mother.

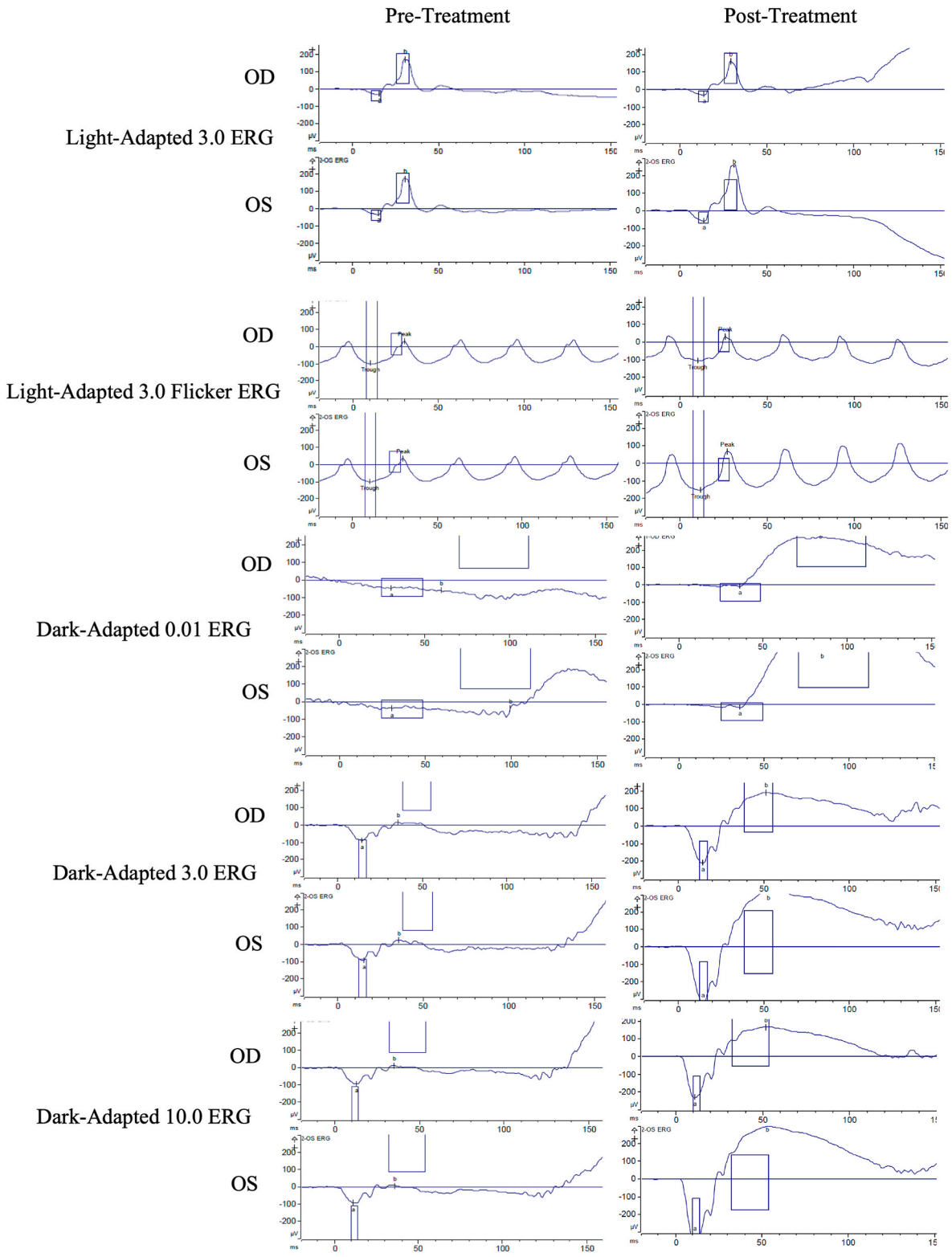

Fig. 2. *Electroretinogram (ERG) Testing Results Pre- and 2 Months Post- Vitamin A supplementation.* (Left) Note latency of B-wave responses in Photopic Flicker ERG, as well as diminished A- and B-wave responses bilaterally during scotopic responses prior to vitamin A supplementation. (Right) Restoration of responses following Vitamin A supplementation.

DEXA scan demonstrated low bone mineral density for age and 24-h urine collection demonstrated hypercalciuria (442 mg/day, normal <200 mg/day) and he was started on thiazide diuretic to mitigate hypercalciuria. The patient's mother was found to be a carrier of the same c.2152C>T (p.Arg718*) variant in *CLCN5* and genetic counseling was performed.

On repeat ophthalmologic exam 2 months following initiation of vitamin A supplementation, the patient reported resolution of nyctalopia. Retinal imaging and exam remained unremarkable. Repeat full-field ERG demonstrated restoration of normal a- and b-wave responses

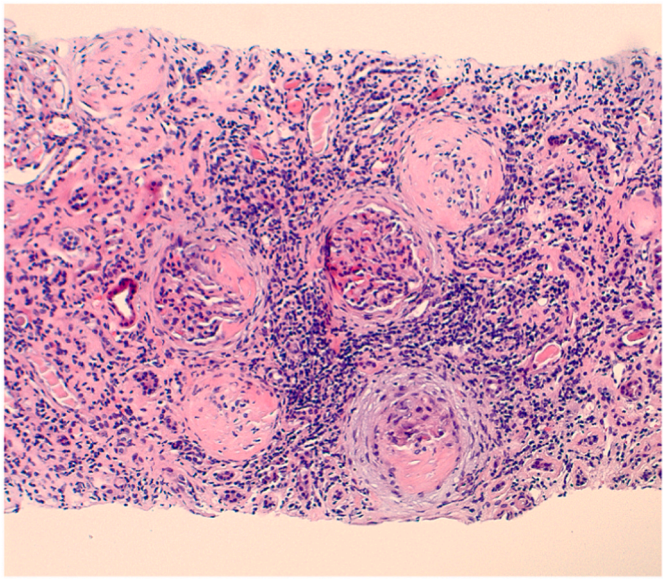

Fig. 3. *Renal Biopsy.* Histopathology demonstrating five globally sclerotic glomeruli, one glomerulus with fibrous crescent (low right), one glomerulus with segmental sclerosis (left middle) and interstitial fibrosis/tubular atrophy (PAS stain).

under both photopic and scotopic conditions (Fig. 2).

3. Discussion

Dent Disease is an X-linked genetic disorder of the proximal renal tubule characterized by a triad of low-molecular-weight proteinuria, hypercalcuria, and nephrocalcinosis and/or nephrolithiasis resulting from pathogenic variations in *CLCN5* (Dent Disease 1), or *OCRL1* (Dent Disease 2), the latter of which is characterized by the same clinical triad in addition to mild intellectual disability, hypotonia, and/or cataract formation[10,15] Lowe Syndrome, also known as oculocerebrorenal syndrome, is also represented by mutations in *OCRL1*, but features clinical manifestations including early cataract formation and brain manifestations that some argue are either a distinct clinical entity or represent the more severe form of the Dent Disease 2 spectrum.[16,17] Due to the X-linked nature of Dent Disease, it has been almost exclusively described in males; however, females, may develop mild proteinuria or hypercalcuria, presumably due to X-chromosome lyonization.[17]

CLCN5 encodes the protein CIC-5, a chloride channel located in renal proximal tubular cells. It is hypothesized that CIC-5 aids in acidification of early endosomes and transport of megalin and cubulin to the apical surface of proximal tubular cells; megalin facilitates reabsorption of low-molecular weight proteins, including retinol binding protein, from the glomerular filtrate.[11,18,19] Deficient or dysfunctional Clc-5 results in proteinuria via a decreased ability for proximal tubular cells to endocytose intraluminal proteins. As RBP-retinol complexes are freely filtered at the proximal tubule, it is hypothesized that this mechanism is responsible for urinary loss of RBP and consequently VAD in Dent Disease.[9,12,20]

Typically, tubular proteinuria is the most common presenting manifestation of Dent Disease, accompanied by symptoms of polydipsia and polyuria.[21] Among younger children, urinary losses of calcium, phosphorous, and vitamin D result in prolonged deficiencies in these substances and can result in rickets, a developmental bone disease that manifests short stature, bony deformities, and increased risk of fractures.[22] Progression to end-stage renal failure occurs in 30–80% of patients by the fifth decade of life and is thought to be attributed in part to nephrocalcinosis, although rate of eGFR decline and progression of nephrocalcinosis have not been consistently correlated.[11,23,24] Glomerular disease, typically glomerular sclerosis as opposed the crescentic pattern observed in our patient, has been reported to result in glomerulosclerosis, which is similar to the biopsy findings seen in our case.[21,25]

The c.2152C>T (p.Arg718*) variant of *CLCN5*, as seen in our patient, is a sequence change that creates a premature stop signal in gene translation. This variant has been observed previously in other individuals with Dent disease, for whom VAD was not recognized, and the disease was detected at a younger age than our patient; further, experimental studies have shown that this sequence affects CLCN5 function.[26–30] As such, despite not being listed in population databases (GnomAD), this variant was classified as pathogenic for X-linked Dent Disease by the CLIA certified laboratory who performed the testing.

Vitamin A is a fat-soluble molecule and is dependent on water-soluble carriers. In blood circulation, it is transported in the form of all-trans-retinol bound to a 21kDa carrier plasma retinol-binding protein 4 (RBP4), which is further bound to 55kDa transthyretin (TTR).[31] In addition to filtration at the proximal tubule, the holo-RBP4:TTR complex diffuses from the choroidal blood circulation through Bruch's membrane and binds to the RBP4 receptor on the RPE cells, named stimulated by retinoic acid 6 (STRA6).[32] STRA6 facilitates the uptake of all-trans-retinol into RPE cells, where 11-cis-retinol is then bound by a cellular retinaldehyde-binding protein (CRALBP) and is oxidized to 11-cis-retinal for use in the visual cycle.[33] As a result, reduced RBP4 levels may result in reduced all-trans-retinal in the visual cycle. It is unclear why rods may be more affected by a loss of RBP4. However, cone photoreceptors are postulated to have an alternative Müller glia dependent recycling method utilizing 11-cis-retinol which may mean that they may be less affected.[34] However, eventually if RBP4 levels remain chronically low, even cone photoreceptors may become affected, as shown by the perturbed cone-dominated 30Hz flicker responses seen in our case.

Nyctalopia is infrequently cited as a symptom associated with Dent Disease. Sethi et al. reported a series of 3 Indian pediatric patients with Dent Disease who presented at an early age with polyuria and polydipsia, who also exhibited nyctalopia that was responsive to vitamin A supplementation.[12] They speculated that urinary wasting of RBP was a cause of VAD, though neither urine nor serum RBP levels were measured among their cohort. Ophthalmological examinations including electroretinogram testing were normal in all three patients in this case series. In another cohort of 8 patients with known diagnoses of Dent disease, Becker-Cohen et al. reported that vitamin A deficiency was present in six (75%) patients, with clinical symptoms of night blindness described in three patients.[9] Funduscopic examination was normal in all patients, and only one patient was found to have Bitot's spots. None of the patients underwent electroretinogram testing in this series. Among patients with VAD, serum RBP concentrations were significantly decreased, and urinary RBP concentrations were found to be elevated in all patients in this cohort. Further, other studies have reported urinary wasting of RBP in other proximal tubulopathies, though to our knowledge clinical VAD has not been reported from other such causes.[35] Of note, our patient represents a unique case in that laboratory correlates of renal disease and proteinuria were discovered or worked up following ophthalmic symptoms, as opposed to the above cases where Dent Disease had already been established. Our patient was also found to have markedly increased urinary RBP levels, although his serum RBP level interestingly was normal, perhaps due to either decreased glomerular filtration rate or measurement following vitamin A supplementation.

To the authors' knowledge, our case is the first to report nyctalopia as the only presenting chief complaint of Dent Disease, without featuring other typical systemic symptoms, such as polyuria, polydipsia, nephrocalcinosis, nor stigmata of rickets or growth delay. Further, it is the first to demonstrate rod-cone dysfunction on full field ERG testing in a patient later diagnosed with Dent disease causing VAD. Similar to other cases, our patient reported rapid resolution of nyctalopia within weeks of starting vitamin A supplementation, and normalization of full field

ERG findings were demonstrated after vitamin A repletion.

Acquired VAD has been demonstrated to have effects on both retinal examination and function. Funduscopic findings have been reported as multiple yellow-white opacities within the macula.[36] Studies using macular OCT have demonstrated focal disruption of photoreceptor outer segments, generalized macular thinning responsive to treatment, and reduction in ganglion cell layer thickness.[37] On ERG, correlates of VAD are better observed in scotopic than photopic conductions, and can include reduced or undetectable rod response, reduced amplitude of cone responses, delayed cone response latency, or absent *S*-cone responses. Rod-cone dysfunction can improve within 3 days of vitamin A supplementation.[36] In our patient, clinical ophthalmological examination was normal; however, abnormal full field ERG findings prompted a work-up for VAD that eventually led to the diagnosis of Dent disease.

The reason that nyctalopia was observed in our patient without other stigmata of Dent Disease remains unclear. Studies that have attempted to associate phenotypic variation with particular *CLCN5* variants have proved inconclusive, relaying that there are no clear phenotype-genotype interactions of disease.[11] In summary, this report is the first describing nyctalopia as the presenting feature in Dent disease without systemic symptoms, expanding the spectrum of phenotypic variability in this tubulopathy.

4. Conclusions

Here, we present a unique case of nyctalopia in a 16-year-old male patient, later found to have abnormal electroretinogram findings and VAD secondary to renal tubular wasting of RBP in Dent Disease. This case highlights the importance of keeping Dent disease and possibly other renal tubular disorders in the differential diagnosis of VAD. Identification of our patient's underlying pathophysiology not only aided in treatment of the chief complaint of nyctalopia, but also identified renal pathology for which early identification and treatment may prevent future systemic complications and morbidity.

Patient consent

The authors have obtained written consent from both the patient's legal guardian to present and publish the above information in this case.

Acknowledgements

SB is funded by a Foundation Fighting Blindness Career development award and a Nixon Vision Foundation award.

The following authors have no financial disclosures as it pertains to this case: JA, AL, SY, RM, LT, CC, KST, SB.

All authors attest that hey meet the current ICMJE criteria for authorship.

The authors would like to acknowledge Gregory Ostrow, MD (Department of Ophthalmology, Rady Children's Hospital, San Diego) for his crucial work in our patient's care.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajoc.2022.101781.

References

1. Sommer A Xerophthalmia. Keratomalacia and nutritional blindness. *Int Ophthalmol*. 1990;14:195–199.
2. Imdad A, Mayo-Wilson E, Herzer K, Bhutta ZA. Vitamin A supplementation for preventing morbidity and mortality in children from six months to five years of age. *Cochrane Database Syst Rev*. 2017;2017, CD008524.
3. Whitcher JP, Srinivasan M, Upadhyay MP. Corneal blindness: a global perspective. *Bull World Health Organ*. 2001;79:214–221.
4. Reboul E. Absorption of vitamin A and carotenoids by the enterocyte: focus on transport proteins. *Nutrients*. 2013;5:3563–3581.
5. McEachron KR, Downs EM, Schwarzenberg SJ, Chinnakotla S, Bellin MD. Fat-soluble vitamin deficiency is common in children with chronic pancreatitis undergoing total pancreatectomy with islet autotransplantation. *J Pediatr Gastroenterol Nutr*. 2021;72:123–126.
6. Mahmood K, et al. Serum retinol binding protein as an indicator of vitamin A status in cirrhotic patients with night blindness. *Saudi J Gastroenterol Off J Saudi Gastroenterol Assoc*. 2008;14:7–11.
7. Rahi AH. Retinol-binding protein (RBP) and pigmentary dystrophy of the retina. *Br J Ophthalmol*. 1972;56:647–651.
8. Seeliger MW, Wissinger B, Zrenner E, Nagy D, Fischer MD. Effects of serum retinol-binding protein (sRBP) deficiency on development and degeneration of the human retina. *Invest Ophthalmol Vis Sci*. 2009;50:974.
9. Becker-Cohen R, et al. Vitamin A deficiency associated with urinary retinol binding protein wasting in Dent's disease. *Pediatr Nephrol Berl Ger*. 2012;27:1097–1102.
10. Claverie-Martín F, Ramos-Trujillo E, García-Nieto V. Dent's disease: clinical features and molecular basis. *Pediatr Nephrol Berl Ger*. 2011;26:693–704.
11. Tosetto E, et al. Phenotypic and genetic heterogeneity in Dent's disease—the results of an Italian collaborative study. *Nephrol Dial Transplant*. 2006;21:2452–2463.
12. Sethi SK, Ludwig M, Kabra M, Hari P, Bagga A. Vitamin A responsive night blindness in Dent's disease. *Pediatr Nephrol Berl Ger*. 2009;24:1765–1770.
13. Robson AG, et al. ISCEV Standard for full-field clinical electroretinography (2022 update). *Doc Ophthalmol Adv Ophthalmol*. 2022;144:165–177.
14. Giebel LB, et al. Tyrosinase gene mutations associated with type IB ('yellow') oculocutaneous albinism. *Am J Hum Genet*. 1991;48:1159–1167.
15. Hichri H, et al. From Lowe syndrome to Dent disease: correlations between mutations of the OCRL1 gene and clinical and biochemical phenotypes. *Hum Mutat*. 2011;32:379–388.
16. Bökenkamp A, et al. Dent-2 disease: a mild variant of Lowe syndrome. *J Pediatr*. 2009;155:94–99.
17. Dent Disease. Nord https://rarediseases.org/rare-diseases/dent-disease/.
18. Santo Y, et al. Examination of megalin in renal tubular epithelium from patients with Dent disease. *Pediatr Nephrol Berl Ger*. 2004;19:612–615.
19. Nielsen R, Christensen EI, Birn H. Megalin and cubilin in proximal tubule protein reabsorption: from experimental models to human disease. *Kidney Int*. 2016;89:58–67.
20. Norden AG, et al. Tubular proteinuria defined by a study of Dent's (CLCN5 mutation) and other tubular diseases. *Kidney Int*. 2000;57:240–249.
21. Wen M, et al. Next-generation sequencing in early diagnosis of dent disease 1: two case reports. *Front Med*. 2018;5.
22. Annigeri RA, Rajagopalan R. Hypophosphatemic rickets due to Dent's disease: a case report and review of literature. *Indian J Nephrol*. 2009;19:163–166.
23. Lloyd SE, et al. Characterisation of renal chloride channel, CLCN5, mutations in hypercalciuric nephrolithiasis (kidney stones) disorders. *Hum Mol Genet*. 1997;6:1233–1239.
24. Blanchard A, et al. Observations of a large Dent disease cohort. *Kidney Int*. 2016;90:430–439.
25. Wang X, et al. Glomerular pathology in dent disease and its association with kidney function. *Clin. J. Am. Soc. Nephrol. CJASN*. 2016;11:2168–2176.
26. Carballo-Trujillo I, et al. Novel truncating mutations in the ClC-5 chloride channel gene in patients with Dent's disease. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2003;18:717–723.
27. Grand T, et al. Novel CLCN5 mutations in patients with Dent's disease result in altered ion currents or impaired exchanger processing. *Kidney Int*. 2009;76:999–1005.
28. Mansour-Hendili L, et al. Mutation update of the CLCN5 gene responsible for dent disease 1. *Hum Mutat*. 2015;36:743–752.
29. Szczepanska M, et al. Dent disease in children: diagnostic and therapeutic considerations. *Clin Nephrol*. 2015;84:222–230.
30. Hureaux M, et al. High-throughput sequencing contributes to the diagnosis of tubulopathies and familial hypercalcemia hypocalciuria in adults. *Kidney Int*. 2019;96:1408–1416.
31. Kanai M, Raz A, Goodman DS. Retinol-binding protein: the transport protein for vitamin A in human plasma. *J Clin Invest*. 1968;47:2025–2044.
32. Kawaguchi R, et al. A membrane receptor for retinol binding protein mediates cellular uptake of vitamin A. *Science*. 2007;315:820–825.
33. Sundaram M, Sivaprasadarao A, DeSousa MM, Findlay JB. The transfer of retinol from serum retinol-binding protein to cellular retinol-binding protein is mediated by a membrane receptor. *J Biol Chem*. 1998;273:3336–3342.
34. Wang J-S, Kefalov VJ. The cone-specific visual cycle. *Prog Retin Eye Res*. 2011;30:115–128.
35. Bernard AM, Vyskocil AA, Mahieu P, Lauwerys RR. Assessment of urinary retinol-binding protein as an index of proximal tubular injury. *Clin Chem*. 1987;33:775–779.
36. McBain VA, et al. Functional observations in vitamin A deficiency: diagnosis and time course of recovery. *Eye Lond. Engl.* 2007;21:367–376.
37. Berkenstock MK, Castoro CJ, Carey AR. Outer retina changes on optical coherence tomography in vitamin A deficiency. *Int. J. Retina Vitr*. 2020;6:23.