Congenital stationary night blindness linked to a CACNA1F gene mutation

Cegueira noturna estacionária congênita associada a uma mutação do gene CACNA1F

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How to cite:
Medina FM, Martins VJ, França FB, Cunha IA, Carvalho GT. Congenital stationary night blindness linked to a CACNA1F gene mutation. Rev Bras Oftalmol. 2025;84:e0021.

doi:
https://doi.org/10.37039/1982.8551.20250021

ABSTRACT

Congenital stationary night blindness encompasses a heterogeneous group of inherited retinal dystrophies characterized by impaired scotopic vision from birth. This article provides a comprehensive overview of congenital stationary night blindness, focusing on its genetic underpinnings, clinical manifestations, and diagnostic approaches, with a specific emphasis on variants in the *CACNA1F* gene. Through a detailed case report of a 49-year-old male with congenital stationary night blindness attributed to a hemizygous variant in *CACNA1F*, we illustrate typical clinical presentations and correlate them with underlying genetic abnormalities. The discussion highlights the importance of integrating advanced diagnostic techniques, such as optical coherence tomography and electrophysiological testing, with genetic analysis for accurate diagnosis and personalized management strategies. Additionally, the genotype-phenotype correlations underscore the significance of genetic screening in predicting disease severity and guiding therapeutic interventions. This article contributes to the understanding of congenital stationary night blindness pathophysiology and emphasizes the role of genetic evaluation in facilitating targeted approaches for diagnosis, familly counseling, and potential future gene therapies.

Keywords:
Night blindness; Night vision; Eye diseases, hereditary; Tomography, optical coherence; Genetic testing; Retinal dystrophies; Patient acuity; Counseling; Genetic therapy

RESUMO

A cegueira noturna estacionária congênita abrange um grupo heterogêneo de distrofias retinianas hereditárias caracterizadas por visão escotópica prejudicada desde o nascimento. Este artigo fornece uma visão abrangente da cegueira noturna estacionária congênita, com foco em suas bases genéticas, manifestações clínicas e abordagens diagnósticas, com ênfase específica nas variantes no gene *CACNA1F*. Por meio de um relato de caso detalhado de um homem de 49 anos com cegueira noturna estacionária congênita atribuído a uma variante hemizigótica de *CACNA1F*, ilustramos apresentações clínicas típicas e as correlacionamos com anormalidades genéticas subjacentes. A discussão destaca a importância da integração de técnicas avançadas de diagnóstico, como a tomografia de coerência óptica e os testes eletrofisiológicos, com a análise genética para um diagnóstico preciso e estratégias de manejo personalizadas. Além disso, as correlações genótipo-fenótipo sublinham a importância do rastreio genético na previsão da gravidade da doença e na orientação de intervenções terapêuticas. Este artigo contribui para a compreensão da fisiopatologia da cegueira noturna estacionária congênita e enfatiza o papel da avaliação genética na facilitação de abordagens direcionadas para diagnóstico, aconselhamento familiar e potenciais terapias genéticas futuras.

Descritores:
Cegueira noturna; Visão noturna; Oftalmopatias hereditárias; Tomografia coerência óptica; Testes genéticos; Distrofias retinianas; Gravidade do paciente; Aconselhamento; Terapias genéticas

Received on:
Jun 10, 2024

Accepted on
Dec 31, 2024

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Conflict of interest:
no conflict of interest.

Financial support:
no financial support for this work.

INTRODUCTION

Congenital stationary night blindness (CSNB) is a heterogeneous group of inherited retinal dystrophies characterized by impaired scotopic vision from birth. Patients with CSNB typically experience difficulties with night vision and navigating in low-light conditions, but unlike progressive retinal diseases, the symptoms of CSNB do not worsen over time. This group of disorders is primarily distinguished by its genetic causes and associated electrophysiological anomalies, with implications for both visual function and retinal structure.

Congenital stationary night blindness can be classified into two main types based on the pattern of visual impairment and electrophysiological findings: type 1 (CSNB1) and type 2 (CSNB2). Congenital stationary night blindness type 1 is typically associated with a negative electroretinogram (ERG), indicating a disruption in the signal transmission from photoreceptors to bipolar cells. In contrast, type 2 is characterized by a normal or reduced b-wave in the ERG, suggesting a defect at the bipolar or ganglion cell level. This classification not only aids in diagnosis but also correlates with different genetic variants affecting specific pathways in the retinal circuitry.

The variants responsible for CSNB are found in genes encoding proteins crucial for the function of photoreceptors or the synaptic transmission between photoreceptors and bipolar cells. Among these, the *CACNA1F* gene is a significant contributor, especially to CSNB2 cases. *CACNA1F* encodes the α1F subunit of the voltage-dependent L-type calcium channel located in the photoreceptor synaptic terminals.[1] Variants in *CACNA1F* disrupt calcium influx, which is essential for the release of neurotransmitters to the bipolar cells, leading to impaired image processing under low light conditions.

Recent development in genetic research have broadened our understanding of CSNB. Studies have revealed a wide spectrum of variants in the *CACNA1F* gene, each contributing differently to the disease phenotype. These variants range from missense and nonsense variants to more complex genomic rearrangements.[2,3] Furthermore, research into the cellular mechanisms affected by these variants shows that altered calcium channel functionality leads to varied effects on retinal cell communication and visual signal processing.[4] Additional studies have shown that variants in *CACNA1F* are associated with optic atrophy and inner retinal thinning, which contribute to the overall phenotype of CSNB.[5]

Moreover, the phenotypic variability observed in CSNB patients, including differences in visual acuity and field defects, reflects the underlying genetic diversity. This variability underscores the importance of personalized genetic diagnostics as a component of comprehensive ophthalmic evaluation and management in CSNB.[6]

CASE REPORT

A 49-year-old male reported lifelong difficulties with night vision and blurry distance vision, stating no progression in symptoms since childhood. The patient's family history was negative for similar visual impairments. Examination revealed a corrected visual acuity of 20/40 in both eyes with a refractive error of -1.00 diopters in the right eye and -0.50 diopters in the left eye. The anterior segment and intraocular pressures were within normal limits. Fundoscopic examination identified pale optic discs, peripapillary atrophy, and macular retinal pigmentary changes in both eyes (Figure 1A). Foveal autofluorescence imaging demonstrated a notable hyperautofluorescent halo, suggestive of abnormal retinal pigment epithelium metabolism or composition (Figure 1B). Detailed optical coherence tomography (OCT) scans indicated a generalized reduction in retinal thickness, particularly in the macular region (Figure 2A) and a thinning of the nerve fiber layer across both eyes (Figure 2B). Visual field analysis showed diminished sensitivity predominantly in the superior and inferior nasal regions of both eyes, with additional loss in the superior temporal region of the left eye. Electrophysiological testing revealed significantly reduced amplitudes in both the scotopic and photopic phases and prolonged latencies, indicating disrupted signal transmission within the retina (Figure 3). Genetic testing confirmed the hemizygous pathogenic variant c.3436C>T (p.Gln1146*) in the *CACNA1F*, corroborating the diagnosis of CSNB.

DISCUSSION

The *CACNA1F* gene encodes the α1F subunit of the voltage-dependent L-type calcium channel pivotal in the phototransduction pathway within the retinal photoreceptors. Variants in this gene lead to dysfunctional calcium channels, which disrupt the normal phototransduction cascade crucial for converting light into electrical signals in the retina. This dysfunction manifests clinically as night blindness and other visual impairments.

Recent literature underscores the diversity of clinical manifestations associated with *CACNA1F* variants. Studies have shown these variants result in a spectrum of ocular phenotypes, from mild myopia to severe retinal degeneration.[2] Furthermore, innovative research using

Figure 1. Color fundus photography and autofluorescence. (A) Color fundus photography showing pale optic disc, peripapillary atrophy, and macular pigmentary changes. (B) Autofluorescence imaging of the foveal region displaying hyperautofluorescence.

transgenic models has demonstrated potential therapeutic benefits of gene therapy, where targeted expression of normal *CACNA1F* in mouse models rectified morphological and functional retinal abnormalities.[4] Additional research has explored the molecular biology underlying the accelerated degradation of variant Cav1.4 channels, suggesting new avenues for pharmacological intervention.[5] Studies have also highlighted the presence of optic atrophy and inner retinal thinning in patients with *CACNA1F* variants, providing further insight into the clinical spectrum of the disease.[6]

Moreover, large cohort studies have reinforced the importance of genetic screening in CSNB, highlighting the frequent involvement of *CACNA1F* variants in these conditions.[3] This genetic insight is crucial not only for accurate diagnosis but also for family planning and management of the condition.

Our case involves a 49-year-old male diagnosed with CSNB linked to a hemizygous variant in the *CACNA1F* gene. This is the first reported case of the hemizygous pathogenic variant c.3436C>T (p.Gln1146*) associated with CSNB, marking a significant addition to the medical literature. This case aligns with the broader findings

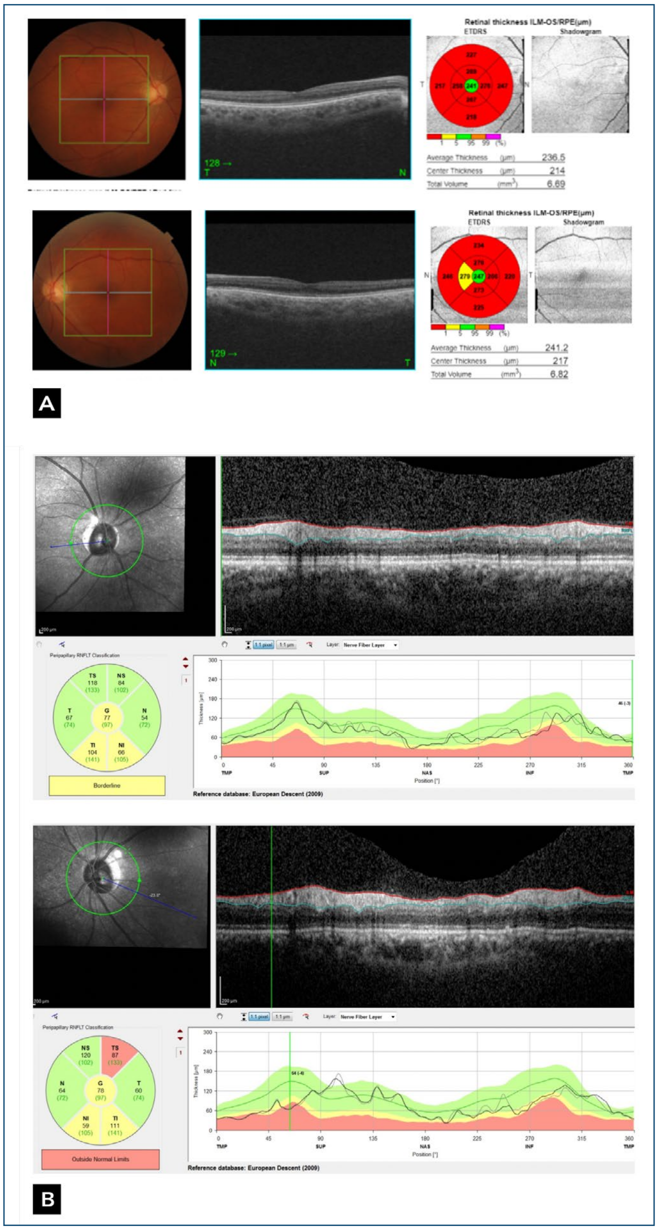

Figure 2. Optical coherence tomography of the macular region and nerve fiber layer. (A) Optical coherence tomography of the macular region showing retinal thinning. (B) Optical coherence tomography imaging of the nerve fiber layer demonstrating decreased thickness.

documented in medical literature, displaying both typical and unique aspects of the condition. Patients with CSNB due to *CACNA1F* variants typically present with night blindness from an early age, similar to our patient who reported lifelong symptoms. Visual acuity among these patients can vary widely; however, our patient's visual acuity of 20/40 is relatively common and reflects a moderate impact of the genetic variant on photoreceptor function.

Fundoscopic findings in our patient included pale optic discs and macular pigmentary alterations consistent

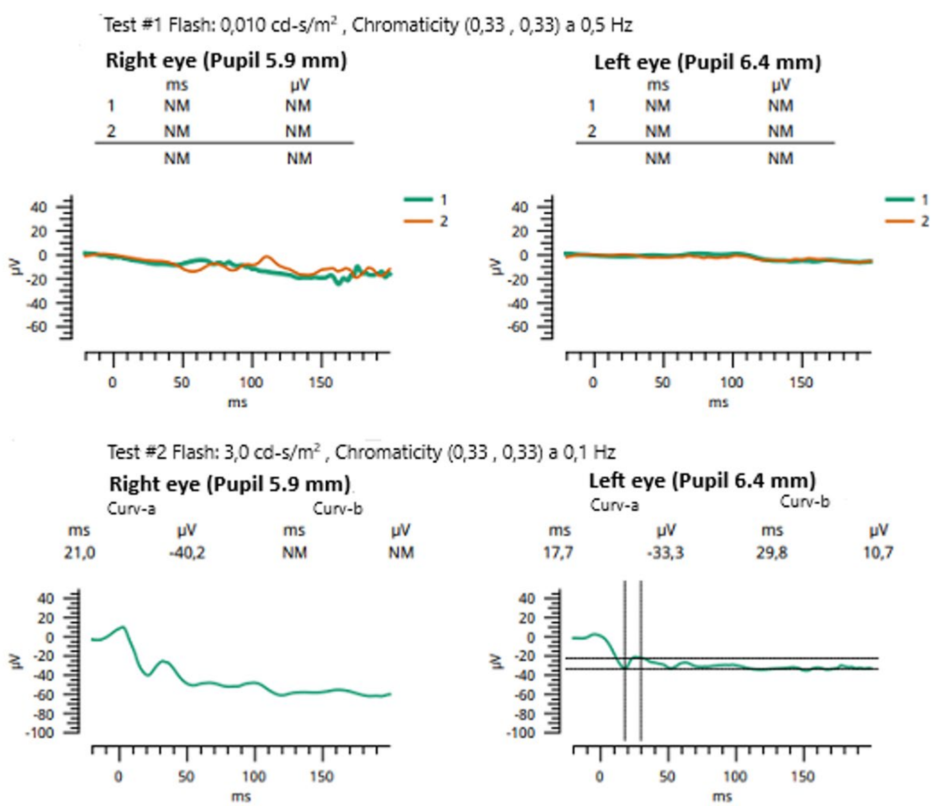

Figure 3. Electroretinography showing reduced amplitude and increased latency.

with those observed in other cases of CSNB2 associated with *CACNA1F* variants. These retinal changes underscore the variant characteristic impact on retinal structure as reported in several studies.[3] Leahy et al. describes optic atrophy and inner retinal thinning in patients with *CACNA1F*-related CSNB, which is consistent with the findings in our case.[6] Our patient exhibited pale optic discs and macular pigmentary changes, aligning with the optic atrophy described in the study. Additionally, the OCT scans in our case revealed a generalized reduction in retinal thickness and thinning of the nerve fiber layer, mirroring the previously reported inner retinal thinning.

The variant identified in our patient, c.3436C>T, is known to disrupt calcium channel activity that is crucial for neurotransmitter release at photoreceptor synapses. This disruption is central to the pathophysiology of CSNB, as detailed by Waldner et al.[4]

The phenotype associated with the CACNA1F gene variant causing CSNB is primarily characterized by congenital night blindness, optic atrophy, and inner retinal thinning. Similar to other forms of CSNB, the CACNA1F variant leads to difficulties with vision in low-light conditions from birth and specific anomalies in ERG patterns, with the condition being non-progressive. However, differences include distinct genetic mechanisms, where CACNA1F affects L-type calcium channels in photoreceptors, while other genes like NYX and GRM6 impact different proteins in synaptic transmission between photoreceptors and bipolar cells. Additionally, CACNA1F variants result in extra retinal abnormalities such as optic atrophy and inner retinal thinning, observed through OCT scans. The severity and specific manifestations of visual impairment can vary significantly depending on the type of genetic variant within the CACNA1F gene, emphasizing the importance of genetic screening and personalized diagnostics.

The severity of clinical symptoms in CSNB can often be correlated with the specific type of variant in the *CACNA1F* gene. More disruptive variants, such as frameshift or nonsense variants, generally result in more severe visual dysfunction compared to missense variants.

Understanding the genetic basis of CSNB not only aids in accurate diagnosis but also influences family counseling and management strategies. It opens the door to potential treatments such as gene therapy, which are currently under exploration in clinical trials and experimental models. These treatments aim to correct the genetic defects at the molecular level, potentially restoring normal function to retinal cells and improving visual outcomes.

Variant gene can lead to various phenotypes by altering protein function or expression. In the case of a patient with a hemizygous variant in the CACNA1F gene, a sequence change creates a premature translational stop signal (p.Gln1146*), resulting in CSNB. This nonsense mutation truncates the α1F subunit of the voltage-dependent L-type calcium channel, crucial for photoreceptor synaptic transmission. Consequently, the patient exhibits lifelong difficulties with night vision and other visual impairments, as the disrupted calcium channels prevent proper neurotransmitter release in the retina, affecting scotopic vision from birth without progressive deterioration.

This case highlights the critical role of comprehensive ophthalmic and genetic evaluations in diagnosing CSNB linked to *CACNA1F* variants. The integration of advanced diagnostic technologies, such as detailed OCT scans and electrophysiological testing, with genetic analysis provides a conclusive diagnosis and facilitates tailored management strategies for patients. The identification of a hemizygous *CACNA1F* variant in this patient underscores the importance of genetic screening in CSNB, enabling accurate diagnosis and informing family planning. Ongoing research into the genetic mechanisms and potential gene therapies offers hope for more effective treatments in the future.

AUTHORS' CONTRIBUTION

Medina FMC and Carvalho GT developed the conception and design of the study and were in charge of the analysis and interpretation of results, writing and critical review of the manuscript content. Martins VJG, França FB and Cunha IAT were in charge of the analysis and interpretation, writing and critical review of the manuscript content. All authors have approved the final version of the manuscript and are responsible for all aspects of it, including ensuring its accuracy and integrity.

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