Unilateral buphthalmos in a patient with short stature: a rare case of dual recessive disorders

Buftalmia unilateral em paciente com baixa estatura: um caso raro de duas condições autossômicas recessivas

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ABSTRACT

Bupthalmos is characterized by congenital enlargement of the eyeball due to uncontrolled glaucoma in early childhood, which is mostly caused by primary congenital glaucoma. Primary congenital glaucoma, the leading cause of childhood glaucoma, is typically inherited in an autosomal recessive manner and is a significant contributor to pediatric blindness. In contrast, cartilage-hair hypoplasia, another autosomal recessive disorder, presents with disproportionate short stature, increased malignancy risk, and immunological complications. This case report describes a rare co-occurrence of primary congenital glaucoma and cartilage-hair hypoplasia in a Brazilian male child. The patient underwent surgical management for primary congenital glaucoma before one year of age, but molecular diagnosis was delayed until eight years of age during an osteochondrodysplasia evaluation. This case underscores the utility of next-generation sequencing in identifying atypical phenotypes and multiple genotypes within a single patient. The presence of two autosomal recessive conditions highlights the importance of comprehensive genetic testing for accurate diagnosis, early clinical intervention, and informed genetic counseling. Families with such conditions should be counseled on the potential for four distinct genotype combinations in future offspring, emphasizing the need for tailored genetic and clinical management strategies.

RESUMO

Buftalmo é caracterizado pelo aumento do globo ocular decorrente de glaucoma não controlado na primeira infância, sendo causado, na maioria dos casos, pelo glaucoma congênito primário. O glaucoma congênito primário, principal causa de glaucoma na infância, é tipicamente herdado de forma autossômica recessiva e constitui uma importante causa de cegueira pediátrica. Em contraste, a hipoplasia de cartilagem-cabelo, outra condição autossômica recessiva, manifesta-se com baixa estatura desproporcionada, aumento do risco de neoplasias e complicações imunológicas. Este relato de caso descreve a rara ocorrência concomitante de glaucoma congênito primário e hipoplasia de cartilagem-cabelo em um paciente do sexo masculino, brasileiro. O paciente foi submetido ao manejo cirúrgico do glaucoma congênito primário antes de um ano de idade, porém o diagnóstico molecular foi realizado aos oito anos, durante investigação de osteocondrodisplasia. Este caso reforça a utilidade do sequenciamento de nova geração na identificação de fenótipos atípicos e múltiplos genótipos em um único paciente. A presença de duas condições autossômicas recessivas destaca a importância da investigação genética abrangente para o diagnóstico preciso, a intervenção clínica precoce e o aconselhamento genético fundamentado. Famílias com tais condições devem ser orientadas quanto à possibilidade de quatro combinações genotípicas distintas na prole futura, enfatizando a necessidade de estratégias personalizadas de manejo genético e clínico.

INTRODUCTION

Congenital glaucoma represents a chronic and significant cause of global blindness.[1] Primary congenital glaucoma (PCG), the most prevalent childhood subtype, is typically characterized by an autosomal recessive inheritance pattern. The prevalence of this condition varies significantly depending on the level of consanguinity within different populations. In communities where consanguineous marriages are common, such as Slovakian Roma (gypsies), Saudi Arabians, and certain Southern Indian populations, the prevalence is notably higher, ranging from 1 in 1,250 to 1 in 3,300 live births.[2,3] In contrast, where consanguinity is less frequent, they report a much lower prevalence, typically between 1 in 10,000 and 1 in 30,000 live births. The overall incidence spans a wide range, from 1:1,250 to 1:3,000, reflecting the influence of genetic and demographic factors.

The pathogenesis involves mutations in several genes, including *CYP1B1, LTBP2,* and *MYOC*. [4-5] Among these, *CYP1B1* plays a critical role in anterior segment development and is strongly associated with the characteristic goniodysgenesis observed in PCG. [6]

Cartilage-hair hypoplasia (CHH) is a pleiotropic autosomal recessive disorder with core manifestations of metaphyseal dysplasia and significant short stature. While most patients are diagnosed in the first year of life due to significant short stature, the phenotype is highly variable. This ranges from isolated proportionate short stature to a more severe presentation combining a skeletal dysplasia with immunodeficiency and an increased risk of lymphoma. Although a founder effect in the *RMRP* gene accounts for a uniform genotype in populations like the Finnish, diverse *RMRP* mutations have been reported, including in a recent Brazilian cohort. [7,8]

The diagnostic availability of next-generation sequencing (NGS) is crucial for such rare disorders, as it enables the precise identification of pathogenic variants, which is the definitive step for confirming a diagnosis and guiding management.

The research was carried out as part of the institute's ongoing commitment to advancing medical knowledge and improving patient care in the field of rare diseases and genomic medicine.

This study was approved by the Instituto Nacional de Saúde da Mulher, da Criança e do Adolescente Fernandes Figueira (IFF/Fiocruz) Ethical board under the registrations ID 1.557.698. All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards as per Brazilian 466/12 National Ethics Resolution.

CASE REPORT

We report an 8-year-old Brazilian boy with CHH phenotype and a rare association with PCG, present since birth. Sanger sequencing of the *RMRP* gene confirmed the presence of a compound heterozygote genotype associated to CHH. Furthermore, exploring the potential diagnostic value of an NGS clinical exome panel, the patient's DNA also revealed association with a compound heterozygote genotype for the *CYP1B1* gene commonly described in cases of primary glaucoma type 3. [1-8] The CHH genotype previously identified by Sanger sequencing was confirmed.

A 3-year and 4-month-old boy was referred to our outpatient genetics clinic for investigation of severe short stature and congenital glaucoma. The pregnancy was uneventful, though no prenatal ultrasonography was performed. A pediatric ophthalmologist diagnosed with PCG at birth, performing two surgical interventions at 3 and 6 months of age. Despite these procedures, the right eye progressed to *phthisis bulbi*. The left eye developed buphthalmos with increased corneal and axial diameters, resulting in persistent glaucoma, high myopia, and astigmatism.

His short stature was not investigated until 2 years and 9 months of age, when a wrist X-ray revealed delayed bone age.

According to our clinical evaluation, the patient's height was significantly compromised (Z-score < -4.6 SDS, WHO growth charts). Ophthalmic findings included right *phthisis bulbi* and left buphthalmos (Figure 1A). Systemic dysmorphic features comprise a flattened nasal bridge, short chest, rhizomelic limb shortening, brachydactyly, *genu-varum*, lordosis, joint hyperlaxity, and thin-sparse hair (Figures 1B to 1D). Despite severe visual impairment, his motor and intellectual development were age appropriate.

There was no relevant family history or consanguinity. The clinical presentation suggested two distinct entities: PCG and a skeletal dysplasia, with CHH as the primary suspect. Subsequent radiographs confirmed metaphyseal dysplasia without spinal involvement (Figure 1E). The patient had no evidence of immunodeficiency or Hirschsprung disease. [9]

The ophthalmic surgery was performed at an external service prior to our evaluation. Consequently, the surgical details and long-term monitoring data are not available in institute records.

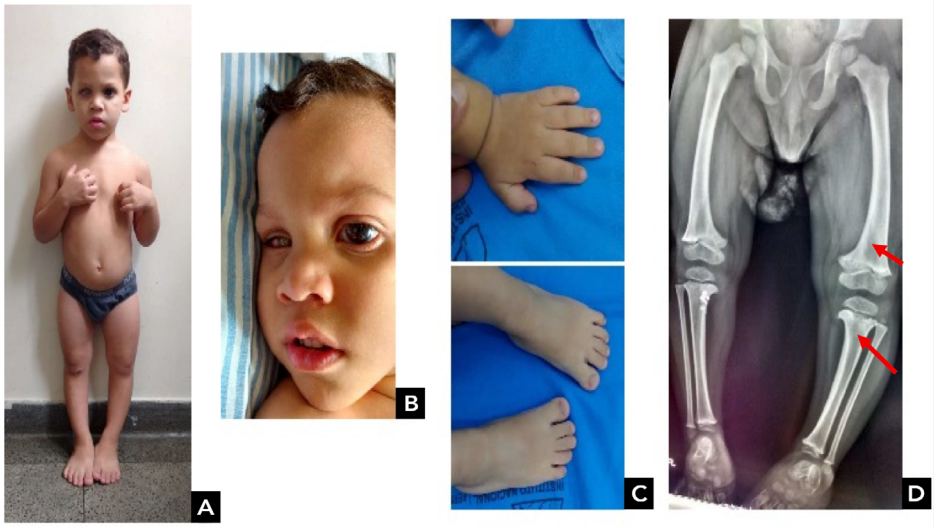

Figure 1. Dysmorphic features. (A) short chest; rhizomelic limb shortening and genu-varum; (B) Right phthisis bulbi and left buphthalmos, flattened nasal bridge, thin-sparse hair; (C) brachydactyly on left hand and feet; (D) anteroposterior radiography of lower limbs shows metaphyseal changes with flaring and lucent zones in the distal femoral and proximal tibial metaphysis (arrows) diaphysis. Femoral and tibial shortened with mild bowing.

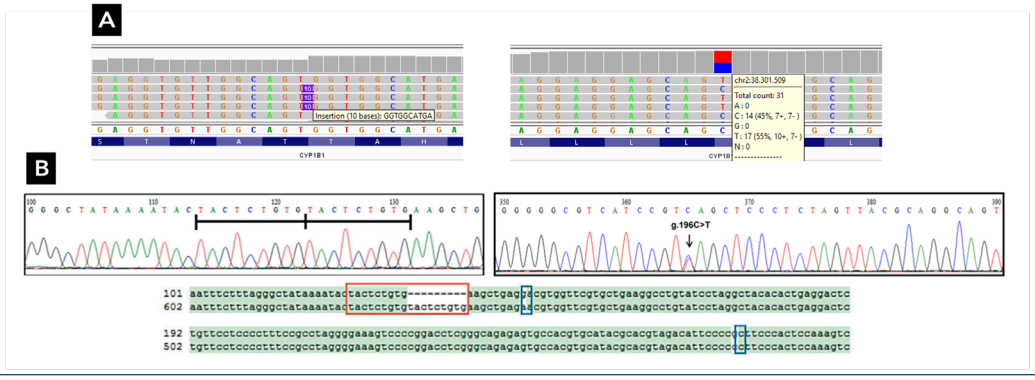

Figure 2. Two heterozygous variants were identified suggesting a compound heterozygote genotype in both genes CYP1B1 (PCG*) and RMRP (CHH*). (A) Integrative genomic viewer image indicating the position of the variants identified through the clinic exome panel: variant CYP1B1: -c.1200_1209 dup(TGGCATGAGG); p.Thr404fs c.1023G>A; p.Trp341Ter (arrow). (B) Representative electropherogram after allele discrimination of the RMRP gene: a duplication of a 9- bp promoter fragment g. –22_– 14dup9 TACTCTGTG combined with a point mutation in the transcribed region (g.196C>T). Alignment of the reference RMRP sequence with the sequence of the allele that contains the 9-bp duplication in the promoter region (red rectangle). Blue rectangles mark polymorphisms.

The patient returned to our unit for follow-up consultation in 2020 and 2025. He did not have any complaints that indicated any comorbidity related to CHH diagnoses. His height was 101 cm (Z score < -4,6 SDS). An ophthalmological examination was also performed, which identified atrophy of the right eye, myopia, astigmatism, and vertical nystagmus in the left eye apart from the glaucoma.

The patient's clinical status at 12 years of age was characterized by satisfactory systemic health. The ophthalmological examination revealed a phthisic right globe and a buphthalmic, glaucomatous left eye (Figure 1F). Glaucoma in the left eye was controlled with a topical regimen of latanoprost 0.005% nightly and dorzolamide twice daily. Anthropometric evaluation confirmed severe short stature, with a height Z-score of -4.67 SDS.

The molecular analysis was initially performed for the promoter and transcript region of the *RMPR* gene. The results were confirmed in the second amplification product.

From the analysis, two pathogenic changes compatible with the clinical diagnosis of CHH were found. The patient revealed two *in trans* pathogenic variants: a duplication in the regulatory region [n. -22_-13dup9(TACTCTGTG)] at the paternal allele and a single nucleotide substitution (n.197C>T) in the transcribed region of the maternal allele (Figure 2A). To investigate potential genetic variants associated with PCG (OMIM 231300), the same proband's genomic DNA sample was analyzed using NGS.

Data processing and analysis took place from the Varstation platform, based on the genes described most frequently associated to PCG (*CYP1B1, LTBP2, MYOC, COL1A1, FOXC1, TEK, PITX2, PAX6, OPTN and TBK1)*. Two heterozygous variants were identified in *CYP1B1* gene, suggesting a compound heterozygote genotype: [c.1200_1209dup (TGGCATGAGG); p. Thr404fs*30] and not yet disease-associated (c.1023G>A; p. Trp341Ter) variant (Figure 2B). Both were confirmed through *Sanger* sequencing. To infer phase information, parental samples were analyzed and revealed that the duplication was inherited from father, and the point variant had a maternal origin.

DISCUSSION

Primary congenital glaucoma is characterized by elevated intraocular pressure originating in the intrauterine period, leading to the classic presentation of buphthalmos. The disease is often bilateral, with a slight male predominance, and arises from defective aqueous humor outflow, frequently linked to mutations in genes such as *CYP1B1*.[7] The specific *CYP1B1* genotype identified has been associated with a severe early onset phenotype, consistent with the presentation at birth.[7,8] The disease pathogenesis is caused by disrupt neural crest cell migration during ocular development, leading to trabecular meshwork dysgenesis and impaired aqueous humor drainage. This results in elevated intraocular pressure, optic nerve damage, and irreversible vision loss if left untreated. The specific *CYP1B1* genotype identified in our patient has been associated with a severe phenotype and early onset, consistent with his presentation at birth. [7]

Conversely, CHH is a rare metaphyseal dysplasia caused by *RMRP* gene variants, characterized primarily by severe short stature and a variable spectrum of extra skeletal manifestations.[9-11]

The co-occurrence of these two distinct autosomal recessive disorders in a single individual is exceptionally rare. This presented a significant diagnostic challenge and raised the possibility of a dual genetic diagnosis. From an ophthalmological perspective, this case underscores a critical clinical insight: the presence of significant systemic findings, particularly severe short stature in a patient with PCG, should not be dismissed as incidental. It should instead prompt a comprehensive genetic evaluation for a possible syndromic cause beyond the primary ophthalmological diagnosis.

The confirmation of two independent molecular etiologies compound heterozygosity for *RMRP* and *CYP1B1* mutations carries significant implications for both genetic counseling and long-term clinical management. Since each autosomal recessive disorder independently confers a 25% recurrence risk for future pregnancies, comprehensive genetic testing is essential to provide accurate reproductive risk assessment and guide family planning decisions.

As primary specialists in the evaluation of congenital glaucoma, ophthalmologists are uniquely positioned to recognize syndromic features that warrant a genetic investigation.[12] The extended use of NGS, especially for heterogeneous and overlapping phenotypes, moves the field beyond the *"lumping versus splitting"*[13] clinical dilemma and is foundational to a precise and personalized medicine. Crucially, an earlier molecular diagnosis can guide proactive interventions to prevent severe, irreversible complications.

This model ensures that a precise molecular diagnosis extends beyond nosology, delivering tangible impacts on patient care. In the present case, the diagnosis was instrumental in guiding a multidisciplinary follow-up for the patient's specific comorbidities.

Ultimately, this synergistic approach transforms a molecular finding into a lifelong care strategy, simultaneously safeguarding the patient's future through clinical and surgical management and empowering the family with the knowledge for informed reproductive decisions.

AUTHORS' CONTRIBUTION

Juan Clinton Llerena Júnior: conceptualization, provision of patient samples and data, manuscript writing and clinical management of the patient. Maria Eduarda Gomes, Natana Chaves Rabelo and Sayonara Maria de Carvalho Gonzalez: responsible for all molecular analysis, genotyping, data curation, Sanger confirmation writing and review of the manuscript. Tatiana Sa Pacheco Carneiro Magalhaes: manuscript writing, review, and manuscript edition.

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