Clinical and Genetic Spectrum of Pediatric IRDs in Portugal: Data from the IRD-PT Registry

Espectro Clínico e Genético das IRDs Pediátricas em Portugal: Dados do Registo IRD-PT

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ABSTRACT

INTRODUCTION: Inherited retinal dystrophies (IRDs) are a major cause of childhood blindness, but to date, no national population-based study regarding the clinical and genetic spectrum of these disorders has been conducted. Thus, this study aimed to characterize the clinical and molecular spectrum of pediatric IRDs in Portugal.

METHODS: Multicenter, cross-sectional, cohort study of consecutive 79 pediatric patients (age < 18 years old), 70 of which unrelated, with a clinical diagnosis of IRD and available genetic testing results, identified via the IRD-PT registry. Phenotype parameters included age of onset, first visual symptom and clinical phenotype based on ophthalmological examination and deep phenotyping. Genetic testing was clinically oriented in all probands and included Sanger sequencing, next-generation sequencing (NGS) or whole exome sequencing (WES)-based panels. Variants were classified in accordance with the American College of Medical Genetics and Genomics (ACMG). Only pathogenic (class V) or likely pathogenic (class IV) variants were considered to establish a molecular diagnosis.

RESULTS: A genetically confirmed diagnosis was achieved in 56/70 (80.0%) families. The most prevalent diagnoses were rod-cone dystrophy (RCD) in 15 patients and cone/cone-rod dystrophy (COD/CORD) in 14 patients. Leber congenital amaurosis (LCA) and albinism were observed in 7 subjects each, X-linked retinoschisis (XLRS) in 6, Usher syndrome in 6, Best disease and achromatopsia in 4 each, Bardet-Biedl syndrome (BBS) in 3, Stickler syndrome, congenital stationary night blindness (CSNB) and Heimler syndrome in 2, and Stargardt disease (STGD), Kearns-Sayre syndrome (KSS), Cohen syndrome, hypotrichosis with juvenile macular dystrophy (HJMD), methylmalonic aciduria (MMA), Liberfarb disease and neuropathy, ataxia and retinitis pigmen-

tosa (NARP) syndrome in 1 subject each. Almost 2/3 (65.8%) of patients initiated symptoms before 6 years old, with nystagmus and vision loss being the most frequently reported symptoms. A total of 59 disease-causing variants were identified distributed across 34 different genes, with *ABCA4* (n=5 families) and *RS1* (n=5) being the most frequently mutated genes.

CONCLUSION: Our results shed light on the clinical and genomic landscape of pediatric IRDs in Portugal. The fact that the majority of children-initiated symptoms before 6 years old highlights the importance of a high level of suspicion to establish an early diagnosis.

KEYWORDS: Child; Genetic Diseases, Inborn; Genetic Testing; Retinal Dystrophies/genetics.

RESUMO

INTRODUÇÃO: As distrofias hereditárias da retina (IRDs) são uma das principais causas de cegueira infantil, mas existe escassez de informação relativa à doença nesta faixa etária. Assim, este estudo pretendeu caracterizar o espectro clínico e genotípico destas patologias em Portugal.

MÉTODOS: Estudo multicêntrico, transversal, que incluiu 79 doentes (70 não relacionados) pediátricos (idade < 18 anos) com diagnóstico clínico de IRD e resultado genético disponível, identificados através do registo *IRD-PT*. Os parâmetros fenotípicos incluíram idade de início, primeiro sintoma visual e fenótipo clínico. Todos os testes genéticos foram clinicamente orientados e incluíram *Sanger sequencing*, painéis de *next generation sequencing* (NGS) ou painéis baseados em *whole exome sequencing* (WES). As variantes foram classificadas de acordo com o American College of Medical Genetics and Genomics (ACMG), e apenas aquelas patogénicas (classe V) ou provavelmente patogénicas (classe IV) foram consideradas para confirmação de diagnóstico molecular.

RESULTADOS: Obteve-se um diagnóstico molecular em 56/70 (80,0%) famílias. Os diagnósticos mais frequentes foram distrofia de cones-bastonetes (RCD) em 15 doentes e distrofia de cones/cones-bastonetes (COD/CORD) em 14. Amaurose congénita de Leber (LCA) e albinismo foram observados em 7 indivíduos cada, retinosquisis ligada ao X (XLR) em 6, síndrome de Usher em 6, doença de Best e acromatopsia em 4 cada, síndrome de Bardet-Biedl (BBS) em 3, síndrome de Stickler, cegueira noturna estacionária congénita (CSNB) e síndrome de Heimler em 2, e doença de Stargardt (STGD), síndrome de Kearns-Sayre (KSS), síndrome de Cohen, hipotricose com distrofia macular juvenil (HJMD), acidúria metilmalónica (MMA), doença de Liberfarb e síndrome de neuropatia, ataxia e retinite pigmentosa (NARP) em 1 doente cada. Quase 2/3 (65,8%) dos indivíduos iniciaram sintomas antes dos 6 anos de idade; os sintomas mais frequentemente relatados foram nistagmo e diminuição da visão. Um total de 59 variantes causadoras de doença foram identificadas, distribuídas por 34 genes, sendo os genes *ABCA4* (n=5 famílias) e *RS1* (n=5) os mais frequentes.

CONCLUSÃO: Os nossos resultados iluminam o panorama clínico e genotípico das IRD pediátricas em Portugal. O facto de a maioria das crianças iniciar os sintomas antes dos 6 anos realça a importância de um elevado nível de suspeição para estabelecer um diagnóstico precoce.

PALAVRAS-CHAVE: Criança; Doenças Genéticas Inatas; Distrofias da Retina/genética; Testes Genéticos.

INTRODUCTION

IRDs comprise a large group of clinically and genetically heterogeneous diseases, with disease-causing variants identified in over 277 genes, affecting different retinal regions and resulting in complex visual impairment phenotypes.[1] These conditions have an overall prevalence of 1 in 3000 individuals,[2,3] and are responsible for a great proportion of childhood blindness, thus posing a high social and economic burden.[4-6] In fact, the British Childhood Visual Impairment and Blindness Study 27 found that 16% of childhood visual impairments were due to IRDs, a similar figure as the one reported in an Australian study.[8] However, in a recent study conducted at a tertiary low vision center in Israel, IRDs were responsible for up to 28% of childhood visual impaiment.[9]

In approximately 20%-30% of cases, the visual complaints can be found as part of a systemic syndrome and

can even represent its first manifestation.[6] Therefore, establishing an early and correct diagnosis based on retinal phenotype can be crucial to prompt adequate management of the systemic disorder.[6]

Furthermore, in the era of gene therapy, high level of clinical suspicion and timely diagnosis are increasingly important,[3] and assessing the epidemiological, genetic and clinical profile of these disorders is crucial for effective disease management (including the recently approved first gene therapy – voretigene neparvovec), genetic counseling and development of new targeted interventions and therapies.[6] In the particular case of pediatric patients, early diagnosis is essential to initiate visual rehabilitation during the appropriate developmental window.[5,6] Moreover, assessing the clinical and molecular profiles may help identify disease modifiers and predict disease progression.

Molecular spectrum and genotype-phenotype correlations in IRDs have been widely studied in different populations and ethnic groups[1,2]; however, these works tend to include mainly adult patients, with children representing only a minor proportion.[10] To date, no national population-based study has been conducted.

Considering the lack of information regarding genotypes and phenotypes of childhood-onset IRDs in Portugal, this study aimed to characterize the clinical and molecular spectrum of these disorders using a web-based, nationwide clinical registry – the IRD-PT (GER Portugal).[11]

METHODS

STUDY DESIGN AND PATIENT SELECTION

An observational, cross-sectional, cohort study was conducted at the following Portuguese centers specialized in IRDs: Centro Hospitalar e Universitário de Coimbra (CHUC); Centro Hospitalar e Universitário do Porto (CHUP), and Centro Hospitalar e Universitário de Lisboa Norte (CHULN). Patients enrolled in the IRD-PT registry[11] and fulfilling the inclusion criteria (age <18 years old and a clinical diagnosis of a syndromic or non-syndromic IRD with available genetic testing results), were included in the study.

The study was approved by the local Ethics Committees and followed the tenets of the Declaration of Helsinki for biomedical research. Written informed consent was obtained for every included subject, with parental consent provided on behalf of the children involved in the study.

CLINICAL FEATURES

Clinical phenotype description was based on the findings obtained through ophthalmological examination performed by a pediatric retina specialist, including visual acuity and dilated fundus examination and, whenever possible, complemented by deep phenotyping (color fundus photography, blue-light fundus autofluorescence imaging, spectral-domain optical coherence tomography), visual field testing and electrophysiology testing.

Additional clinical data was collected, namely initial visual symptoms (nystagmus, vision loss, photophobia, night blindness and visual field loss), age of onset (determined as the age at which the patient or his carriers noticed first visual symptoms), age at diagnosis, and in case of syndromic disease, the timeline of systemic symptoms regarding visual manifestations (precedent, simultaneous or subsequent to visual symptoms). The presence of positive family history and consanguinity were also retrieved from each individual patient file.

GENETIC TESTING

Genetic testing was clinically-oriented in all probands and included Sanger sequencing in cases of clinically pathognomonic phenotypes or those strongly suggestive of mutations in one specific gene (eg. XLRS); next-generation sequencing (NGS) IRD panels for features suggesting phenotypes associated with a limited panel of genes; or whole exome sequencing (WES)-based panels for very genetically heterogenous phenotypes. Whenever possible, confirmatory segregation analysis was performed on family members. Variants were classified in accordance with the ACMG guidelines.[12] The identification of clinically significant variants, classified as pathogenic (class V) or likely pathogenic (class IV), was required to classify cases as genetically solved. Genetic counselling provided by a medical geneticist was granted to all subjects.

STATISTICAL ANALYSIS

Statistical analysis was performed using the SPSS program (SPSS Statistics, version 15 for Windows, SPSS Inc., IBM, Somers, NY). Descriptive analysis was performed for all study variables. Continuous variables were recorded as mean and standard deviation (SD) values with minimum and maximum when appropriate, whereas categorical variables were recorded as absolute and relative frequencies.

RESULTS

A total of 79 subjects (70 families) with a mean age at diagnosis of 7.3±4.7 years and slight male predominance (n=49; 62.0%), were included. Almost 2/3 (65.8%) presented with visual symptoms within the first 5 years of life, with nystagmus and decreased vision being the most frequent symptoms in this age range. More than 1/5 (n=17, 21.5%) of patients initiated symptoms in the first month. In those presenting after 5 years of age (26.6%), the primary visual symptoms described were decreased vision and night blindness. Only 2 subjects presented an age of onset after 10 years old. Six patients (7.6%) were asymptomatic by the time of the diagnosis (2 patients diagnosed by an ophthalmological routine exam, and 4 diagnosed trough familiar screening in the context of positive family history). Characteristics regarding age of onset and initial symptoms of the study cohort are summarized in Table 1.

Table 1. Characterization of age of onset and initial symptoms of the study cohort.

	Initial Symptom (n)					
Age of onset	**Nystagmus**	**Decreased vision**	**Photophobia**	**Night blindness**	**Asymptomatic**	**Total**
0-1 month	14	2	1	0	-	17 (21.5%)
>1 month-12 months	7	3	1	5	-	16 (20.3%)
13 months- 5 years	1	12	2	4	-	19 (24.1%)
6-10 years	0	14	0	5	-	19 (24.1%)
>10 years	0	0	0	2	-	2 (2.5%)
Asymptomatic	-	-	-	-	6	6 (7.6%)
Total	22 (27.8%)	31 (39.2%)	4 (5.1%)	16 (20.3%)	6 (7.6%)	79 (100%)

A detailed characterization of the phenotypes is summarized in Table 2. The most frequently observed phenotype was rod-cone dystrophy (RCD, n=15 patients), followed by cone/cone-rod dystrophy (COD/CORD, n=14).

All patients diagnosed with LCA, achromatopsia and albinism initiated symptoms in the first year of life, and the majority in the LCA (n=5/7 subjects) and achromatopsia (n=3/4) groups presented with nystagmus in the first

Table 2. Detailed characterization of the phenotypes observed in the study cohort.

Phenotype	Age at diagnosis in years (mean ± pattern deviation)	Main presenting symptom	Consanguinity (% of families)	Genetically solved cases (% of families)	Most frequently mutated genes (number of solved families)
RCD (n=15, 19.0%; 14 families)	9.9±4.2	Night blindness (n=10)	14.3	50.0	*RHO* (2)
CORD/COD (n=14, 17.7%; 11 families)	11.4±3.3	Decreased VA (n=12)	9.1	72.7	*ABCA4* (4)
LCA (n=7, 8.9%; 7 families)	1.3±0.7	Nystagmus (n=7)	14.3	100.0	*NMNAT1* (3)
Albinism (n=7, 8.9%; 6 families)	1.8±2.3	Nystagmus (n=7)	16.7	33.3	*TYR* (3)
XLR (n=6, 7.6%; 5 families)	9.5±2.8	Decreased VA (n=6)	0.0	100.0	*RS1* (5)
Usher syndrome (n=6, 7.6%; 5 families)	5.5±2.8	Night blindness (n=3)	40.0	100.0	*MYO7A* (3)
Best disease (n=4, 5.1%; 3 families)	6.8±2.9	Decreased VA (n=2), asymptomatic (n=2)	0.0	100.0	*BEST1* (3)
Achromatopsia (n=4, 5.1%; 3 families)	4.0±1.2	Nystagmus (n=3)	66.7	100.0	*ATF6* (1) *CNGB3* (1) *CNGA3* (1)
BBS (n=3, 3.4%; 3 families)	8.0±8.0	Decreased AV (n=1), night blindness (n=1), asymptomatic (n=1)	33.3	100.0	*BBS12* (2)
Sickler syndrome (n=2, 2.5%; 2 families)	9.0±6.0	Decreased VA (n=2)	0.0	50.0	*COL2A1* (1)
CSNB (n=2, 2.5%; 2 families)	7.5±1.5	Night blindness (n=1) Nystagmus (n=1)	0.0	100.0	*CACNA1F* (1) *RLBP1* (1)
Heimler syndrome (n=2, 2.5%; 1 family)	4.0±3.0	Night blindness (n=2)	100.0	100.0	*PEX1* (1)
STGD (n=1, 1.3%; 1 family)	8	Photophobia	0.0	100.0	*ABCA4*
KSS (n=1, 1.3%; 1 family)	3	Photophobia	0.0	100.0	DNA mitochondrial deletion involving *NDL4, ND4, tRNAHis, tRNASer2, tRNALeu2* and *ND5* genes
Cohen syndrome (n=1, 1.3%; 1 family)	4	Decreased VA	100.0	0.0	*VPS13B*
HJMD (n=1, 1.3%; 1 family)	4	Decreased VA	100.0	100.0	*CDH3*
MMA (n=1, 1.3%; 1 family)	5	Nystagmus	100.0	100.0	*MMACHC*
Liberfarb (n=1, 1.3%; 1 family)	2	Nystagmus	100.0	100.0	*PISD*
NARP (n=1, 1.3%; 1 family)	5	Decreased AV	0.0	100.0	*MT-ATP6*

RCD – rod-cone dystrophy; CORD/COD – cone-rod dystrophy/cone dystrophy; LCA – Leber congenital amaurosis; XLR – X-linked retinoschisis; BBS – Bardet-Biddle syndrome; CSNB – congenital stationary night blindness; STGD – Stargardt disease; KSS – Kearns-Sayre syndrome; HJMD - hypotrichosis with juvenile macular dystrophy; MMA - methylmalonic aciduria; NARP - neuropathy, ataxia and retinitis pigmentosa syndrome; VA – visual acuity.

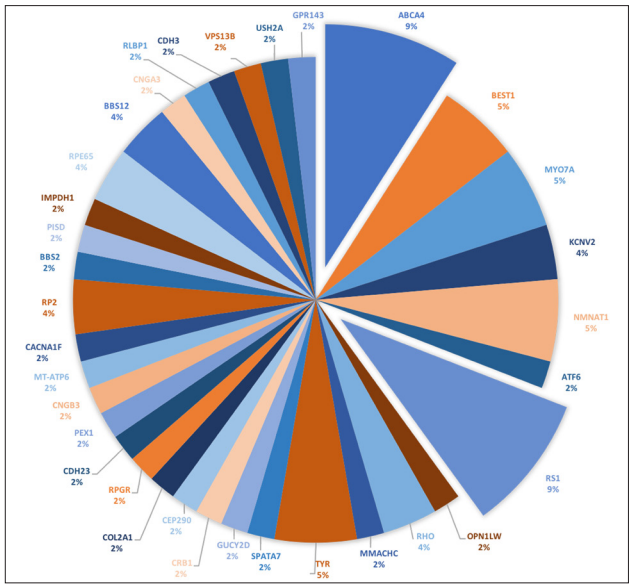

Figure 1. Distribution of the mutated genes observed in the solved cases group.

month. Conversely, in the COD/CORD group, almost 2/3 (64.3%) of patients-initiated symptoms during the scholar age (6-10 years).

Between one-third and one-fourth of patients (n=23, 29.1%) presented associated systemic disorders. In 4 of these cases, a clinical diagnosis was not established by the time of their first ophthalmic evaluation. A detailed characterization of the retinal phenotype prompted further investigation and led to the final diagnosis in 3 cases of Usher syndrome and one case of BBS.

Half of the subjects had a positive family history (n=40, 50.6%), and consanguinity was observed in more than 1/5 of families (n=15, 21.4%), with the highest proportion of consanguinity cases verified in the Usher, Bardet-Biedl and achromatopsia groups (1/3 of families were consanguineous).

A genetically confirmed diagnosis was obtained in 56/70 (80.0%) families. More than half of the unsolved cases (n=8/14, 53.3%) were observed in the RCD group. However, it is noteworthy to mention that in 10 unsolved families, a final molecular diagnosis could not be established due to the presence of at least one variant of uncertain significance (VUS, class III) where the ACMG classification was impossible to change to class IV despite a clear association with the phenotype. Thus, despite the unsolved tag, genetic testing in these 10 families still supported the diagnosis. A total of 59 disease-causing variants were identified across 34 different genes (Fig. 1), 7 of which are novel and herein reported for the first time (Table 3). *ABCA4* (7 patients, n=5 families) and *RS1* (6 patients, 5 families) were the most frequently mutated genes. The following 6 disease-causing variants were observed in more than one family: c.4720G>T (p.Glu1574*) in *ABCA4* gene (2 families), c.577C>T (p.Pro193Ser) in *RS1* (2 families), c.769G>A (p.Glu257Lys) in *NMNAT1* (2 families), c.1205G>A (p.Arg402Gln) in TYR (2 families) and c.316G>A (p.Gly106Arg) in *RHO* (2 families).

Regarding the inheritance pattern, 66.7% of solved cases showed an autosomal recessive pattern, followed by X-linked (20.4%) and autosomal dominant (13.0%).

DISCUSSION

By combining data from 3 national referral University Hospitals from Porto, Coimbra and Lisbon, this is the first study to characterize the clinical and genetic spectrum of pediatric IRDs in Portugal. We identified the most frequent presenting symptoms and described the genetic landscape of these visually incapacitating conditions in a large pediatric cohort. Overall, disease-causing variants were identified in 56/70 families, for a diagnostic yield of 80%. Additionally, 7 novel disease-causing variants are herein reported for the first time.

As observed in other studies,[3,5] low vision and nystagmus were the most frequently reported symptoms in our cohort. This differs from adult IRD cohorts where night blindness is usually the most common symptom.[2,15] The early symptoms observed in children are less suggestive of a specific disease pattern when compared to manifestations described in adult cohorts, where photophobia and visual loss presenting as initial symptoms usually point towards a cone system defect, whereas night blindness would characterize a rod-predominantly disorder.[5,15] These differences can be explained, on the one hand, by the difficulty recognizing some symptoms such as photophobia or night blindness in young children, and on the other hand,

Table 3. Description of the novel disease-causing variants identified in the study cohort.

Gene	Phenotype	Novel variant (nucleotide; protein)	ACMG classification
***ATF6* (NM_007348.4)**	Achromatopsia	c.909+2T>G; p.?	Likely pathogenic
***OPN1LW* (NM_020061.5)**	CORD	c.852C>G; p.(Tyr284*)	Likely pathogenic
***COL2A1* (NM_001844.4)**	Stickler syndrome	c.3186del; p.(Ala1063Leufs*67)	Pathogenic
***CDH23* (NM_022124.5)**	LCA	c.768+2T>A; p.?	Likely pathogenic
***RP2* (NM_006915.3)**	RCD	c.22del; p.(Phe75Leufs*16)	Likely pathogenic
***RLBP1* (NM_000326.5)**	CSNB	c.348del; p.(Tyr117Metfs*2)	Likely pathogenic
***GPR143* (NM_000273.3)**	Albinism	c.14G>T; p.?	Pathogenic

CORD – cone-rod dystrophy; COD – cone dystrophy; LCA – Leber congenital amaurosis; RCD – rod-cone dystrophy; CSNB – congenital stationary night blindness.

by the hypothesis of a more aggressive and diffuse nature of the early onset IRDs, compromising both cone and rod systems from an early disease stage.[5] It is also noteworthy to mention that almost 2/3 (65.8%) of children evaluated in our study initiated symptoms before school age, and 40.8% presented their first manifestation in the first year of life. This is a key information to family physicians, pediatricians and parents/caregivers in order to allow a swift patient referral in the presence of nystagmus and/or lack of visual behavior.

RCD is consistently reported as the most prevalent IRD in adult patients,[2,16] a fact that has also been observed in the Portuguese adult population.[11] However, the distribution of IRDs in pediatric cohorts seems to differ across populations and age groups. In a study conducted in Italy evaluating a cohort with an age of onset <5 years,[3] achromatopsia was the most common diagnosis (n=28/68), followed by RCD (n=9/68); in an Emirati cohort with onset < 16 years old,[13] CORD phenotypes were the most frequent (n=29/71), whereas a study in New Zealand (onset < 16 years)[10] mentioned RCD as the most common diagnosis (n=40/159). In our population <18 years, RCD was the most frequent phenotype, observed in 15/79 patients (19.0%). Although this figure sits between those previously described,[3,10] it is considerably inferior to that observed in the Portuguese adult cohort,[11] where ~50% families presented this phenotype. It seems that cone-dominant disease (14/71 cases in our cohort) is more prevalent in pediatric IRDs, which can be attributed to an earlier onset/diagnosis of these phenotypes compared to rod-predominant IRDs.[13,17]

Almost 1/3 of patients presented a syndromic condition, a proportion significantly higher than the one referred in one study conducted in the UK,[14] where only 14% of cases were accompanied by systemic manifestations, but similar to that reported in adult patients.[1] Despite all syndromic subjects presented already systemic manifestations by the time of their ophthalmic evaluation, 4 of them did not have an established diagnosis. In these cases, the ocular findings triggered further investigation that led to the final diagnosis (3 cases of Usher syndrome and 1 BBS). This clearly highlights the importance of ophthalmic examination to guide the diagnosis of certain systemic genetic disorders.

In this study, a diagnostic yield of 80.0% was obtained. This is similar to the one described in other studies that analyzed the molecular landscape of pediatric and/or adult IRD cohorts in the NGS era.[3,10,17,18]

The most commonly mutated gene in our cohort was *ABCA4* (5/70 families, 7.1%), responding for four CORD cases and one STGD case. These results support those presented in other studies that point to *ABCA4* as the most frequently mutated gene in both pediatric and adult patients, with frequencies varying from 10.4% to 29.8%.[10,17-19]

Interestingly, we found a high prevalence of disease-causing variants in the *NMNAT1* gene (3/7 LCA families), which contradicts the low percentage (1% or less) of LCA cases that has been attributed to this gene in the literature.[25-27] However, the aggressive phenotype that usually characterizes *NMNAT1*-associated disease and the small LCA sample size may be regarded as possible explanations for this unexpected result.

We found 7 novel disease-causing variants in *ATF6*, *OPN1LW*, *COL2A1*, *CDH23*, *RP2*, *RLBP1* and *GPR143* genes, thus expanding the molecular spectrum of disease associated with these 7 genes.

The main limitation of this study is the restricted number of patients in each phenotype group, preventing us to extrapolate further conclusions regarding the genetic spectrum and clinical presentation of each isolated condition, and its differences from the adult phenotypes.

CONCLUSION

This study sheds light on the clinical and genomic landscape of pediatric IRDs in Portugal. A highly satisfactory detection rate of disease-causing genotypes was obtained using clinically-oriented genetic testing. Both low vision and nystagmus, particularly in the first year of life, must prompt appropriate investigation based on a high level of suspicion for IRDs. In four cases, the ophthalmic manifestations dictated the appropriate workup that led to the diagnosis of a systemic condition, allowing its adequate multidisciplinary management. Therefore, it is important to raise awareness among pediatricians, family physicians, parents and general ophthalmologists regarding these rare but impactful conditions in the child development.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

SG: Planeamento e delineação do estudo, colheita e organização dos dados, estatística e escrita do manuscrito.

AM, SVP, ALC, JS, JM e RS: Colheita de dados e revisão do manuscrito.

CP: Colheita de dados, supervisão e revisão do manuscrito.

JPM: Planeamento e delineação do estudo, supervisão, colheita de dados e revisão do manuscrito.

Todos autores aprovaram a versão final a ser publicada.

SG: Planning and design of the study, collection and organization of data, statistics and writing of the manuscript.

AM, SVP, ALC, JS, JM and RS: Data collection and revision of the manuscript.

CP: Data collection, supervision and revision of the manuscript.

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All authors approved the final version to be published.

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