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Ophthalmological evaluation and integrated intervention in a family with congenital aniridia in Alagoas, Brazil

Avaliação oftalmológica e intervenção integrada em família com aniridia congênita em Alagoas, Brasil

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Abstract

***Objective**: We aimed to describe the clinical and phenotypic manifestations as well as the visual prognosis of a family with CA in Northeastern Brazil. **Methods:** This was a cross-sectional study involving 31 individuals (56 eyes) from the same family presenting CA phenotypes. The study population resided in the municipality of Água Branca, in the backlands of the state of Alagoas, Northeastern Brazil. The clinical and phenotypic variables were analyzed. For the analysis, descriptive statistics (absolute and relative frequency and measures of central tendency and dispersion) and inferential statistics (Shapiro–Wilk and Student's t tests) were used, with 95% confidence intervals and significance set at 5%. **Results**: Of the 31 individuals, 18 (58.1%) were male, with a mean age of 27.45 ± 17.49 years, with no difference between sexes. Of the 56 eyes evaluated, 26 and 30 were right and left eyes, respectively; 61.3% (n = 19) individuals had complete bilateral aniridia and 25.8% (n = 8) reported a total loss of light perception in both the eyes. The most prevalent ocular abnormalities were nystagmus (n = 27; 87.09%), cataract (n = 20; 64.5%), strabismus (n = 14; 45.2%), corneal changes such as opacities and/or vascularization (n = 13; 41.93%), and ectopia lentis (n = 6; 19.4%). Further, 13 individuals underwent retinal optical coherence tomography, six man and seven women aged 9–48 (mean, 30.15 ± 15.9) years. All patients presented absence of foveal depression as well as reduced macular thickness and visual acuity. Nine subjects underwent phacoemulsification. **Conclusion:** The study showed wide phenotypic variation among the studied individuals, with poor visual prognosis. The study highlights the need to establish comprehensive care mechanisms for families with the disease.*

Keywords: Aniridia; PAX6 gene; Phenotype; Congenital abnormalities/therapy, Visual acuity

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Resumo

Objetivo: Descrever manifestações clínicas e fenotípicas e o prognóstico visual de uma família com aniridia congênita (AC). **Métodos:** Trata-se de estudo transversal envolvendo 31 indivíduos (56 olhos), de uma mesma família com fenótipo de AC residindo no município de Água Branca, no sertão do estado de Alagoas, região nordeste do Brasil. Foram analisadas variáveis clínicas e fenotípicas. Para a análise, foi utilizada a estatística descritiva (frequência absoluta e relativa e medidas de tendência central e de dispersão) e inferencial (testes de Shapiro-Wilk e t Student). Considerou-se o intervalo de confiança de 95% e a significância de 5%. **Resultados**: Dos 31 indivíduos, 18 (58,1%) eram do sexo masculino, com média de idade de 27,45±17,49, sem diferença entre os sexos. Dos 56 olhos avaliados, 26 eram olhos direitos e 30 olhos esquerdos: 61,3% (n=19) apresentavam aniridia bilateral total; 25,8% (n=8) referiam perda total de percepção da luz em ambos os olhos. As anormalidades oculares mais prevalentes foram o nistagmo (n=27; 87,09%), catarata (n=20; 64,5%), estrabismo 14 (45,2%), alterações opacidades ou vascularização corneanas (n=13; 41,93%) e ectopia lentis (n=6; 19,4%). Os 13 indivíduos submetidos à tomografia de coerência óptica (OCT) retiniana apresentavam perda da depressão foveal, redução da espessura macular e redução da acuidade visual. Nove indivíduos foram submetidos a cirurgia de facoemulsificação. **Conclusão:** O estudo mostrou ampla variação fenotípica entre os indivíduos estudados, com pobre prognóstico visual. O estudo destaca a necessidade de estabelecer mecanismos de cuidado integral para as famílias com a doença.

Descritores: Aniridia, genética, Gene PAX6; Fenótipo, Anormalidades congênitas/ terapêutica; Acuidade visual

Introduction

Congenital aniridia (CA) is a rare genetic disorder that affects about 1:40,000–1:100,000 live births.[1,2] Approximately 2/3th cases are due to autosomal dominant inheritance with high penetrance and variable expressivity, whereas 1/3th cases are sporadic cases due to de novo mutation.[3] The PAX6 gene accounts for approximately 90% of mutations because it is related to the coding of an important transcription factor that is involved in the development of the ocular structures, olfactory structures, central nervous system, and pancreas.[4]

CA is characterized by iris hypoplasia, and in 85% cases, CA is associated with other structural and/or functional ocular abnormalities such as cataract, glaucoma, corneal opacity, lens subluxation, foveal, optic nerve, macular hypoplasia, nystagmus, strabismus, photophobia, and others.[1,5] Therefore, the term "congenital aniridia" has been replaced by "aniridia syndrome.[1] " Although CA may manifest itself in isolation, its presence is detected in 20% patients with Wilms' tumor, aniridia, genital anomalies, and mental retardation (WAGR) syndrome.[6]

This phenotypic heterogeneity observed in individuals with CA has been reported in individuals with the same mutation as well as in those with different mutations.[7,8] The reasons that explain this variability in phenotypes[7] are not yet explained, which makes continuous ophthalmological monitoring essential for the prevention and/or treatment of abnormalities associated with the condition and to improve the quality of life of the affected individuals.

Brazil lacks the accurate epidemiological data regarding the prevalence of this condition in its population, and only few studies have addressed the topic, which are mostly clinical case studies.[9,10] Therefore, investigations with larger populations become relevant because the findings can contribute toward the identification of the problem and implementation of comprehensive care measures for these patients, thus reducing the functional and social impairments caused by this disorder.

Based on these considerations, we aimed to describe the clinical and phenotypic manifestations and the visual prognosis of a family with CA in Northeastern Brazil.

Methods

Study design

This was a cross-sectional observational study.

Population

The study population comprised a family of 31 individuals (56 eyes) with CA. Recruitment began in 2012, with a patient who sought medical care at the Federal University of Alagoas Hospital in the city of Maceió, Brazil. The patient reported the presence of the same phenotypes in other family members. Since then, the researchers from the Federal University of Alagoas and the Federal University of Rio Grande do Sul have developed a research project for the molecular investigation of this family. Genetic mutation in the family was confirmed by genetic testing.[11,12]

The family resided in Água Branca, in the backlands of the state of Alagoas. This municipality has a population of 20,000 and is located 304 km away from the state capital, Maceió (Figure 1).

We included only individuals with total or partial CA, belonging to the five generations of this family. As an exclusion criterion, we adopted the withdrawal of consent, at any time, by any of the individuals.

Study variables

The following variables were assessed: age, gender, CA laterality, corrected visual acuity according to the Snellen decimal scale, iris hypoplasia (total, partial, or absent), microcornea (cornea <10 mm in both meridians), corneal opacity, corneal neovascularization, lens opacification, ectopia lentis, nystagmus, photophobia, strabismus, glaucoma, phthisis bulbi, microphthalmia, and absent foveal reflex.

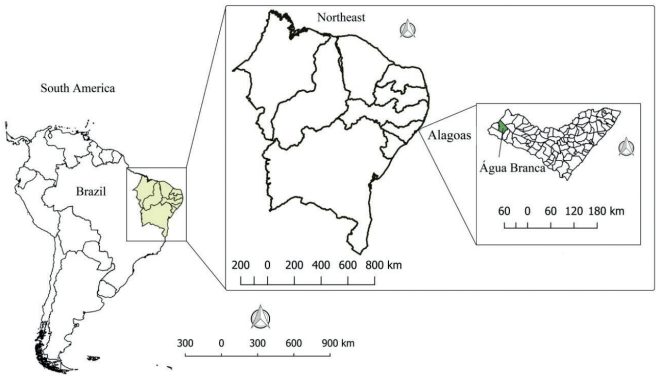


Figure 1: Location map of the study area. Municipality of Água Branca, Alagoas, Brazil.

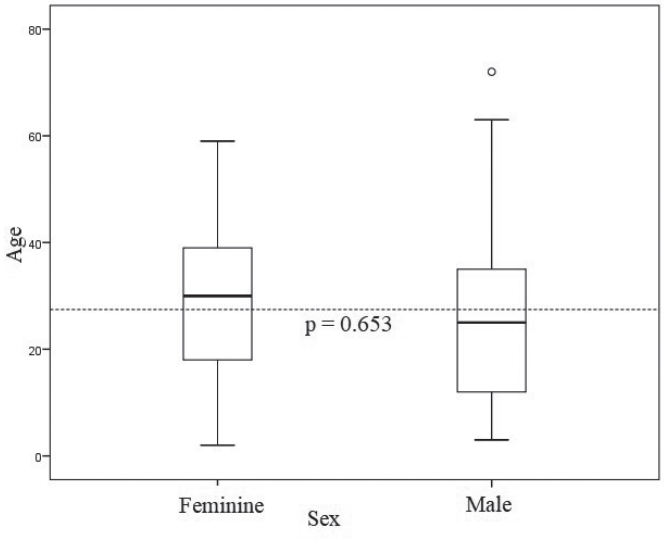


Figure 2: Boxplot of age according to sex of individuals with congenital aniridia.

Data collection procedures

The individuals were invited to participate in the study. Following acceptance, they filled and signed an informed consent form.

Eye examination was performed including the following: a) measurement of corrected and uncorrected visual acuities; b) evaluation of eye movements (presence of strabismus and nystagmus); c) slit-lamp biomicroscopy to evaluate the cornea (presence of microcornea, opacity, and neovascularization), anterior chamber, iris (hypoplasia), and zonule of Zinn and lens (positioning and opacity); d) binocular indirect ophthalmoscopy (loss of foveal reflex); e) gonioscopy (evaluation of the iris root, anterior chamber angle, and trabecular meshwork); f) applanation tonometry for IOP measurement; g) macular evaluation with optical coherence tomography (OCT) CIRRUS SW (v. 6.5.0.772 CARL ZEISS); and (h) corneal pachymetry and specular microscopy for transparent corneas.

Data were collected on two occasions. The first took place in August 2013, when the genetic testing (already published) and ophthalmological evaluation of the family were conducted, whereas the second in March 2019, when the ophthalmology team of the university hospital returned to the municipality for a new ophthalmological evaluation with OCT.

Statistical treatment

Once the data were systematized, statistical analysis was performed. In the descriptive analysis, categorical variables were presented by absolute and relative frequency and continuous variables by central tendency and dispersion measures. Shapiro–Wilk test was used to evaluate data normality. Once the assumption of Gaussian distribution was confirmed, parametric statistics (Student's t test) were used to compare the continuous variables.

Ethical aspects

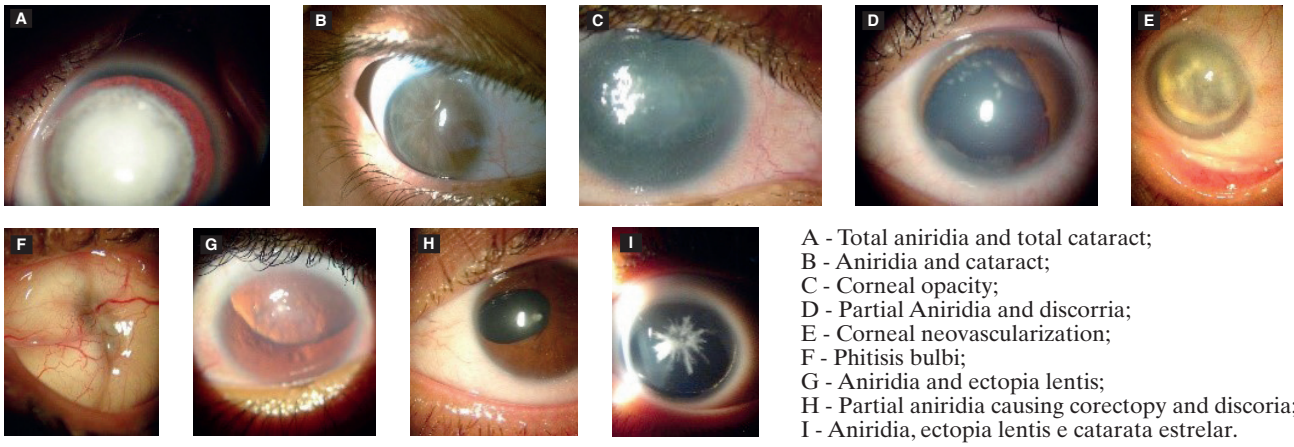
The study was approved by the Federal University of Rio Grande do Sul ethics committee (protocol number 195,023; dated February 7, 2013), with the financial support of INAGEMP (National Institute of Population Medical Genetics). In 2017, the University of São Paulo School of Medicine Ethics Committee for the analysis of research projects was asked to approve the use of secondary data related to the ophthalmological examinations from 2013 and the use of OCT in patients (approval number 1,897,358; dated January 17, 2017).

Results

Of the 31 individuals evaluated, 18 (58.1%) were male and 13 (41.9%) were female. There was a wide variation in age (between 2 and 72 years), with an overall group mean of 27.45 ± 17.49 years. The mean ages of women and men were 29.15 ± 15.71 and 26.22 ± 19.0 years, respectively, with no significant difference (Figure 2).

Of the 56 eyes evaluated, 26 and 30 were right and left eyes, respectively. The ophthalmological evaluation showed that 61.3% (n = 19) individuals had complete bilateral aniridia. Complete unilateral aniridia, partial bilateral aniridia, partial unilateral aniridia, and bilateral misshapen pupils were observed in 12.9% (n = 4) and unilateral misshaped pupil in 6.4% (n = 2) patients (Table 1).

Overall, 25.8% (n = 8) reported complete loss of light perception in both the eyes. The most prevalent eye diseases were nystagmus (n = 27; 87.1%), cataract (n = 20; 64.5%), strabismus (n = 14; 45.2%), corneal alterations such as opacities and/or vascularization (n = 13; 41.9%), and ectopia lentis (n = 6; 19.4%; Table 2). In addition, there were also reduced foveal reflex (three individuals), phthisis bulbi (four individuals), and microphthalmia (five individuals). Figure 3 presents the main ophthalmological findings.



A - Total aniridia and total cataract;
B - Aniridia and cataract;
C - Corneal opacity;
D - Partial Aniridia and discorria;
E - Corneal neovascularization;
F - Phitisis bulbi;
G - Aniridia and ectopia lentis;
H - Partial aniridia causing corectopy and discoria;
I - Aniridia, ectopia lentis e catarata estrelar.

Figure 3: Main ocular findings of individuals with congenital aniridia.

Table 1
Ophthalmological evaluation in an individual with congenital aniridia (n=31)

Eye abnormalities	n	%
Bilateral total aniridia	19	61.3
Unilateral total aniridia	4	12.9
Bilateral partial aniridia	4	12.9
Unilateral partial aniridia	4	12.9
Bilateral misshapen pupils	4	12.9
Unilateral misshapen pupils	2	6.4

Table 2
Eye abnormalities of higher prevalence in individuals with congenital aniridia (n=31)

Eye abnormalities	n	%
Corneal opacities and/or neovascularization	13	41.9
Cataract	20	64.5
Ectopia Lentis	6	19.4
Nystagmus	27	87.1
Strabismus	14	45.2

Table 3
Detailing of ophthalmological evaluation of individuals with congenital aniridia (n=31)

Variables	Right eye		Left eye	
	n (%)	CI 95%	n (%)	CI 95%
Iris				
IMP (Impractical)	4 (12.90)	3.,63-29.83	2 (6.45)	0.79-21.42
PAN (Partial Aniridia)	3 (9.68)	2.04-25.75	4 (16.13)	5.45-33.73
PD (Pupil Disform)	3 (9.68)	2.04-25.75	3 (9.68)	2.04-25.75
TAN (Total Aniridia)	21 (67.74)	48.63-83.32	21 (67.74)	48.63-83.32
Microcornea				
IMP (Impractical)	2 (6.45)	0.79-21.42	2 (6.45)	0.79-21.42
Yes	7 (22.58)	9.59-41.10	10 (32.26)	16.68-51.37
No	20 (64.52)	45.37-80.77	17 (54.84)	36.03-72.68
Not rated	2 (6.45)	0.79-21.42	2 (6.45)	0.79-21.42
Opacity				
IMP (Impractical)	1 (3.23)	0.08-16.70	-	-
Yes	12 (38.71)	21.85-57.81	11 (35.48)	19.23-54.63
No	16 (51.61)	33.06-69.85	18 (58.06)	39.08-75.45
Not rated	2 (6.45)	0.79-21.42	2 (6.45)	0.79-21.42
Neovascularization				
IMP (Impractical)	1 (3.23)	0.08-16.70	-	-
Yes	7 (22.58)	9.59-41.10	8 (25.81)	11.86-44.61
No	21 (67.74)	48.63-83.32	21 (67.74)	48.63-83.32
Not rated	2 (6.45)	0.79-21.42	2 (6.45)	0.79-21.42
Cataract				
IMP (Impractical)	5 (16.13)	5.45-33.73	3 (9.68)	2.04-25.75
Yes	17 (54.84)	36.03-72.68	18 (58.06)	39.09-75.45
No	7 (22.58)	9.59-41.10	8 (25.81)	11.86-44.61
Not rated	2 (6.45)	0.79-21.42	2 (6.45)	0.79-21.42
Ectopia Lentis				
IMP (Impractical)	5 (16.13)	5.45-33.73	4 (12.90)	3.63-29.83
Yes	3 (9.68)	2.04-25.75	6 (19.35)	7.45-37.47
No	21 (67.74)	48.63-83.32	19 (61.29)	42.19-78.15
Not rated	2 (6.45)	0.79-21.42	2 (6.45)	0.79-21.42
Glaucoma				
IMP (Impractical)	9 (29.03)	15.22-48.04	9 (29.03)	15.22-48.04
Yes	3 (9.68)	5.45-33.73	4 (12.90)	3.63-29.83
No	15 (48.39)	30.15-66.94	14 (45.16)	27.32-63.97
Not rated	4 (12.90)	3.63-29.83	4 (12.90)	3.63-29.83
Visual Acuity				
0.05	2 (6.45)	0.79-21.42	1 (3.23)	0.08-16.70
0.25	-	-	1 (3.23)	0.08-16.70
0.3	1 (3.23)	0.08-16.70	-	-
FC (Finger Count)	10 (32.26)	16.68-51.37	11 (35.48)	19.23-54.63
IMP (Impractical)	1 (3.23)	0.08-16.70	1 (3.23)	0.08-16.,70
HM (Hand Movement)	6 (19.35)	7.45-37.47	5 (16.13)	5.45-33.73
LP (Light Perception)	-	-	1 (3.23)	0.08-16.70
NLP (No Light Perception)	9 (29.03)	14.22-48.04	9 (29.03)	12.22-48.04
Not rated	2 (6.45)	0.79-21.42	2 (6.45)	0.79-21.42

Table 4
Detailed optical coherence tomography of individuals with congenital aniridia (n=13)

Individuals	Sex	Age (years)	Mt µm (RE)	Mt µm (LE)
1 *	M	48	Cataract	Cataract
2	F	18	283	214
3	F	40	192	316
4	M	11	240	208
5	F	34	Cataract	Cataract
6	M	25	246	Cataract
7 *	F	36	268	Prosthesis
8 *	F	35	Cataract	Cataract
9	F	35	262	266
10 *	F	24	178	Cataract
11	M	9	304	277
12	M	42	Cataract	Cataract
13	M	35	278	292

Mt- Macular thickness; *Surgery performed in 2019; M- Male; F-Female; RE- Right Eye; LE- Left Eye.

Detailed ophthalmological evaluations stratified by eye showed similar percentages of involvement between the eyes. However, the left eye presented slightly higher percentages than the right eye for the variables microcornea, neovascularization, cataracts, ectopia lentis, and glaucoma (Table 3).

In 2019, aged 9–48 (30.15 ± 15.9) years underwent the retinal (macular) OCT exam. All patients presented absence of foveal depression as well as reduced macular thickness and visual acuity. Macular density was measured in 15 of 26 eyes, nine RE and six RE. Cataract was observed in six patients and 10 eyes (Table 4).

Thereafter, phacoemulsification was indicated for cataract correction for individuals who needed it, five of which were operated in 2013 and four in 2019. The surgeries were performed at the university hospital (two surgeries) and at Instituto da Vision de Maceió (seven surgeries). These surgeries were free of charge to the patients.

In addition, the family received genetic counseling and one member was referred to Escola de Cegos Cyro Accioly (a school for the blind), in Maceió, to learn Braille and act as a multiplier within their family.

Discussion

In this study, male predominance and wide variation in age and intrafamilial phenotypic characteristics were observed. The onset of clinical manifestations occurs during the first years of life, as observed in this study and corroborated by literature.[12,13] The impairment of visual function results in physical, functional, psychological, and social impairments, with consequent reduction in the quality of life of individuals.[12] Therefore, early diagnosis can reduce the effect of the disease on individuals' lives.

The worsening of visual function at an early age and the importance of early medical intervention is shown by Gazzola et al.[14] in an individual with bilateral aniridia and progressive congenital cataract treated at 7 years of age. Surgical treatment comprised phacoemulsification with anterior femtosecond laser capsulotomy, intraocular lens implant, and pars plana vitrectomy combined with posterior capsulotomy. The successful outcome improved the quality of life of this patient. In addition, favorable results with corneal transplantation have also been reported since the 1990s, involving a 10-month-old infant and 35-year-old adult.[15]

In CA, the genotypic and phenotypic variations have been the object of recurrent investigations. A study by Dubey et al7 involving 30 Indian probands and their relatives showed wide genotypic (13 mutations) and phenotypic variation among individuals. In the 19 members from 13 families who had PAX6 gene mutations, the following characteristics were observed: nystagmus (19/19), foveal hypoplasia (18/19), cataract (13/19), glaucoma (9/19), keratopathy (10/19), microcornea (2/19), blepharoptosis (2/19), lens subluxation (2/19), and optic nerve anomalies (2/19).

These results are similar to ours, in which nystagmus, cataract, strabismus, and corneal changes were the most frequently observed changes. The reasons for intrafamilial and interfamilial phenotypic variations are not yet clearly elucidated, supposedly due to the high number of possible mutations.[16,17] In the Indian study,[7] the location and type of mutation was correlated to the phenotypic characteristics of the individuals.

Additionally, 11 new mutations were identified in this study,[7] increasing the number of mutations that had been reported and indicating that other factors, besides PAX6, may also be related to the phenotypic characteristics such as allelic heterogeneity,[2,8,18] multiple interactions and specific gene/allele interactions,[19] modifiers located in the same locus/region of the causal gene,[19,20] and the frequency of modifier variants in the general population.[19,20]

In a study conducted in Russia by Vasilyeva et al.[8] with 117 individuals, of whom 110 had CA and seven had WAGR syndrome, the clinical findings varied in a wide spectrum of phenotypes: complete bilateral aniridia (n = 83; 75.5%), partial aniridia or iris hypoplasia (n = 27; 24.5%), and non-ocular involvement such as changes in the central nervous system, renal neoplasms, and WAGR syndrome.[8] The authors also found wide intrafamilial and interfamilial phenotypic variations.[8] Similar results were observed in a study with 22 Korean individuals from 18 different families, of which 20 presented complete aniridia and two partial aniridia, in addition to cataract (n = 18; 81.8%), foveal hypoplasia (n = 17; 85.0%), glaucoma (n = 7; 31.8%), and other less common findings.[21] As the Korean study and because the present study focused only on eye disorders, we did not investigate any changes in other body systems, a gap to be answered in future studies.

Due to the wide phenotypic variations and unfavorable prognosis, the intervention and treatment process should be early, continuous, and comprehensive. Monitoring the clinical progression and function of the ocular structures, early interventions (whether medical and/or surgical), and social reintegration of individuals whose condition is no longer reversible should be the three pillars of comprehensive care for these patients. In the studied population, living in a city in the Brazilian Northeastern inlands with scarce healthcare resources and in a context of social vulnerability can further compromise the individuals with aniridia.

Besides providing the clinical characterization of the studied population, this study offered medical and surgical treatment and genetic counseling for the family as well as the opportunity to learn Braille free of charge for the subjects.

Conclusion

The ophthalmological evaluation of the family from Água Branca, Alagoas, with CA, featured affected individuals with wide interfamilial and intrafamilial phenotypic variations that were associated with other ocular abnormalities, with poor visual prognosis. These data show that the affected individuals need access

for the management of treatable disorders (congenital cataracts, corneal diseases, and glaucoma) because they are responsible for a significant part of the progressive visual loss that begins in early childhood. Thus, these results highlight the need to have access to comprehensive care for those who are affected as well as for their families.

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