Research Article

Prevalence of consanguinity in non-syndromic paediatric cataract; an experience from an ophthalmology centre in Baghdad

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ABSTRACT

INTRODUCTION: An isolated paediatric cataract is a rare genetic defect of the eye with a high clinical and genetic heterogeneity. It has a very harmful effect on the vision if left untreated at the appropriate time. Autosomal dominance is the commonest mode of inheritance; however, other modes of inheritance are also reported.

OBJECTIVE: to measure the prevalence of consanguinity among parents of patients with non-syndromic paediatric cataracts, identify their demographic features, and find an association between these features and the laterality of involvement of the eyes.

METHODS: A descriptive study with some analytic elements was performed at Ibn Al-Hytham Teaching Eye Hospital between September 2013 and August 2020. We reported the age at presentation, gender, family history of congenital cataract, laterality of the eye involved, parental consanguinity and degree of consanguinity. Associated measure between these demo-social factors and parental consanguinity and laterality of eye involvement. Statistical differences among data were tested by the Pearson chi-square correlation test and the likelihood ratio. P-value <0.05 was considered significant.

RESULTS: Non-Syndromic paediatric cataract is more in males than in females and usually presented in the first year of life. Parents consanguinity was present in 79.4% (181 out of 228) of patients with non-syndromic paediatric cataract. Parental consanguinity has a statistically significant association with bilateral eye involvement than in unilateral eye involvement, p- value 0.001. There was a statistically significant association between having bilateral cataract and a positive family history of paediatric cataract, parental consanguinity, and degree of consanguinity.

CONCLUSION: Parental consanguinity is found in most patients with paediatric cataracts, suggesting that the inheritance of this disease in Iraq is probably autosomal recessive.

Key words: Non-syndromic, paediatric cataract, autosomal recessive, autosomal dominant, Iraq.

INTRODUCTION

A cataract is the opacity of the crystalline lens that causes a limitation of visual function.[1] It can be asymptomatic, especially when the opacity does not involve the visual axis. Paediatric cataract whether congenital or acquired, isolated or associated with systemic/ocular anomalies, is responsible for about ten % of children's vision loss worldwide.[2,3]

Isolated hereditary cataract accounts for about 25% of cases; its morphology, frequency, and the need for surgery are usually similar in parents and offspring. It carries a better prognosis than that associated with ocular or systemic abnormalities.[4] Transparency and a high refractive index of the crystalline lens are achieved by the precise architecture of lens protein and the presence of gap junctions in human lens fibres. Studies on hereditary congenital cataract have identified several classes of genes that encode many lens proteins such as crystalline, lens-specific connexin, aquaporin, cytoskeletal structural protein and developmental regulator.[5,6]

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Early diagnosis of this type of cataract is essential because appropriate intervention can preserve a good visual function. The preferred time for surgery in unilateral congenital cataract is less than six weeks of age and less than eight weeks in bilateral cases.[7] A serious sequela of untreated congenital paediatric cataract is the deprivation amblyopia, a form of reduced vision due to obstruction of the visual pathway during a critical period of maturation of the brain and visual systems thought to occur in the first eight years of life. So, effective screening, early detection, and appropriate timing of surgery for congenital paediatric cataract are of paramount importance.[3,8,9]

A non-syndromic paediatric cataract is a rare genetic mal-development defect of the eye with high clinical and genetic heterogeneity. Most frequently, it is characterized by bilateral symmetrical cataract present at birth or early childhood and not associated with other eye or systemic abnormalities.[10,11]

On clinical genetic bases, consanguineous marriage, common blood, is a union between two individuals who are related as a second cousin or closer with an inbreeding coefficient (F) of 0.0156 and above. Where (F) represents the proportion of loci at which the offspring of a consanguineous union are expected to inherit identical gen copies from both parents.[12] Clinically consanguineous marriage is a relationship between people who share a common ancestor or blood or union contracted between biologically related individuals.[13] Consanguineous marriage is common in Arabic communities; it accounts for 56.4% of marriages. In Baghdad, Iraq, the overall prevalence of consanguineous union is 44.04 %, with a mean inbreeding coefficient of 0.01851. The catalogue of transmission of genetics in the Arab population (CTGA) database has referred that a relative abundance of recessive disorders in the regions is associated with the practice of consanguineous marriage.[13, 14]

In paediatric cataract, all three Mendelian modes of transmission have been reported, but autosomal dominance is the main type of inheritance, accounting for about 75% of them. However, in populations where consanguineous marriage is widely practised, the recessive mode for genetic disorders, including hereditary cataracts, is more common.[15,16]

One-third of the patients with congenital/childhood cataract have a positive family history of hereditary cataract. In many children, the cause of paediatric cataract is not identified.[7,17] Numerous gene mutations affecting crystalline, membrane transport channels, and gap junction proteins were linked to inherited cataract.[18]

During our work in paediatric ophthalmology, we noticed many patients with non-syndromic congenital/paediatric cataract, especially the bilateral ones, are offspring of consanguineous marriages. This phenomenon has driven our interest in studying the link between non-syndromic congenital cataract and consanguineous marriage. We do not have such a study at our centre to our best knowledge.

This study was designed to measure the prevalence of consanguinity among parents of patients with non-syndromic paediatric cataracts, identify their demographic features, and find an association between these features and the laterality of involvement of the eyes.

METHODS

Setting and study design: A descriptive cross-sectional study with analytic elements was performed at Ibn Al-Hytham Teaching Eye Hospital between September 2013 and August 2020.

Ethical consideration: The ethical research committee of the Al-Risafa Health Directorate has approved the study protocol. The official agreement was taken from the hospital administration. Verbal Informed consent of patients' relatives has been taken for all patients enrolled in this study.

Case definition; inclusion and exclusion criteria: In this study, we included patients below the age of 12 years who visited Ibn Al-Haitham hospital during the studied period and were diagnosed with uni or bilateral non-syndromic paediatric cataracts. A non-syndromic cataract

is cataract without other ocular or systemic abnormalities.

Patients who have a history of trauma; ocular abnormalities; chromosomal abnormalities; a positive test for venereal disease research laboratory (VDRL) or toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus (TORCH); abnormal serum levels of calcium, phosphorus, blood sugar, T3, T4, and TSH level; congenital metabolic disorders; and other systemic disorders that can be a cause for secondary cataract were excluded.[2] Genetic testing was not done as it was not available in our country during the study; this was a significant limitation for this study.

Sampling: We included 228 patients (128 male and 110 female) who fulfilled the enrolment criteria conveniently. We selected patients who fulfilled the inclusion criteria and visited the consultancy clinic of the author on Sundays and Thursdays of each week during the period between September 2013 and August 2020.

The procedure: All members involved in this study underwent complete ocular examination, including visual acuity and red reflex for both eyes, simultaneously using a direct ophthalmoscope from a distance of 30cm.[2,19] We examined the anterior segment with pre and post pupillary dilation using cyclopentolate hydrochloride and tropicamide, 0.5 % in patients less than one year of age and 1 % in patients more than one year of age for both medications.[2] We performed the cycloplegic refraction under pupillary dilatation as wet refraction in the childhood period, which is a necessary examination.[20] We measured the cataract density by assessing the red reflex and the fundus view quality before and after pupillary dilation using a direct and indirect ophthalmoscope.[21] Fundus examination was done only in patients in whom the cataract density was not precluding fundus view and red reflex.

Statistical analysis: Statistical was performed via International Business Machine Corp.(IBM) SPSS v20 package for windows 10, New York, USA. Data were presented as frequencies and percents. Statistical differences among data were tested by the Pearson chi-square correlation test and the likelihood ratio. P-value <0.05 was considered significant.

Table 1 | Demo-sociographic features of patients with non-syndromic paediatric cataract (total number = 228).

Features		No.	%
Age (years), Mean ± SD: 1.58 ± 2.5	<1	149	65.4
	1-6	60	26.3
	7-12	19	8.3
Gender	Male	128	56.14
	Female	100	43.86
Laterality	Bilateral	203	89
	Unilateral	25	11
Family History of congenital cataract	Positive	95	41.7
	Negative	133	58.3
Consanguinity	Present	181	79.4
	Absent	46	20.2

RESULTS

A total of 228 patients diagnosed with non-syndromic congenital/childhood cataract were enrolled in this study; 128 (56.14%) were males, and 100 (43.86 %) were females. Most of the patients were diagnosed below the age of one year, 149 (65.4%), then 60 (26.3%) at the age of 1-6 years, and only 19 (8.3 %) at the age of 7-12 years. Bilateral cataract were diagnosed in 203 (89%), and 95 (41.7 %) of pt. had a positive family history of congenital cataract. The rate of consanguineous marriage reported by parents of the patients was 79.4 % (181 out of 228), as shown in table 1.

In all age groups, bilateral cataract are more common than unilateral cataract; however, this association has no statistical significance, p=0.158. Similarly, although bilateral cataract is more common in males and unilateral cataract are reported more in females, these figures have no statistically significant association, p=0.195. Positive Family history of congenital cataract was reported in 93 (40.8 %) patients with bilateral cataract compared to only 2 (0.9%) with unilateral cataracts; this difference has a significant statistical association. Consanguinity marriage was reported in 168 (73.7 %) patients with bilateral congenital cataract compared to 13 (5.7%) for unilateral cataract, with a

Table 2 | Association of socio-demographic features to laterality of eye involvement

Feature		Laterality of eye involvement			P value	Likelihood ratio
		Total case (%)	Bilateral (%)	Unilateral (%)		
Age	<1 yr	149 (65.4)	129 (56.6)	20 (8.8)	0.158	0.057
	1-6 yr	60 (26.3)	55 (24.1)	5 (2.2)		
	7-12 yr	19 (8.3)	19 (8.3)	0 (0)		
Gender	Male	128 (56.14)	117 (91.41)	11 (8.59)	0.195	0.197
	Female	100 (43.86)	86 (86)	14 (14)		
Family History of congenital cataract	Positive	95 (41.7)	93(40.8)	2(0.9)	0.000*	0.000*
	Negative	133 (58.3)	110 (48.2)	23(10.1)		
Consanguinity**	Present	181 (79.4)	168(73.7)	13 (5.7)	0.001*	0.003*
	Absent	46 (20.2)	34 (14.9)	12 (5.3)		
Degree of consanguinity**	None	46 (20.18)	34 (73.91)	12 (26.09)	0.003*	0.009*
	Cousins	127 (50.70)	117 (92.13)	10 (7.87)		
	Relatives	54 (29.83)	51 (94.44)	3 (5.56)		

The total number of the patients included in this study is 228.
* P-value < 0.05 was considered significant.
** The total number of these two features is 227 patients, one patient had a missing data.

p-value of 0.001 and a likelihood ratio of 0.003. See table 2.

Table 3 shows the association between the consanguinity of parents and the demographic and clinical features. It has been found that the patient's age at diagnosis, gender, and family history of congenital cataract have shown non statistically significant association with the consanguinity of the parents. In contrast, laterality of eye involvement and degree of consanguinity have shown a statistically significant association with parents' consanguinity.

DISCUSSION

This study showed that parents' consanguinity was present in 79.4% of the non-syndromic paediatric cataract; this ratio is a bit higher than that reported by Rana from Pakistan in 2014, where parents' consanguinity was present in 69.6% of patients with non-syndromic cataracts.[22] The high rate of parental consanguinity in our and Pakistani studies might indicate that the mode of inheritance of the non-syndromic paediatric cataract in these two populations is autosomal recessive, while most hereditary paediatric cataract show an autosomal dominant mode of inheritance.[2]

We found that 149 (65.4 %) of the patient were diagnosed with congenital paediatric cataract below the age of one year. In contrast, Rana from Pakistan[22] found that 24.4 % of patients were diagnosed below one year. The difference between these studies needs further investigation to disclose whether patients with congenital paediatric cataract in Iraq showing clinical features earlier than those in Pakistan or if it is due to a better search for visual impairment among Iraqi children.

In our series, bilateral non-syndromic paediatric cataract cases were more than unilateral cases, 89% versus 11%, respectively; this result agrees with Rana,[22] where 80.4% of their patients had bilateral eye involvement. In our study, parent consanguinity was found in 168 (73.7%) of the patient with bilateral paediatric cataract compared to only 13 (5.7 %) in patients with unilateral; this difference was statistically significant with a p-value of 0.001. Similarly, Saba and Irshad[23] from Pakistan in 2021 found that 67.01 % of bilateral eye involvement was associated with parents' consanguinity.

We found that males were more commonly involved with paediatric cataract than females, 128 (56.14 %) versus 100 (43.86 %). Gender

Table 3 | Association of some socio-demographic features to parental consanguinity

Features		Consanguinity			P value	Likelihood ratio
		Total case (%)	Present (%)	Absent (%)		
Age	<1 yr	149 (65.4)	115 (77.18)	33 (22.15)	0.803	0.740
	1-6 yr	60 (26.3)	50 (83.3)	10 (16.67)		
	7-12 yr	19 (8.3)	16 (84.21)	3 (15.79)		
Gender	Male	128 (56.14)	104 (81.25)	24 (18.75)	0.427	0.355
	female	100 (43.86)	77 (77)	22 (22)		
Family History of congenital cataract	Positive	95 (41.7)	79 (83.16)	16 (16.84)	0.386	0.319
	Negative	133 (58.3)	102 (76.69)	30 (22.57)		
Laterality	Bilateral	203 (89.04)	168 (82.76)	34 (16.75)	0.001*	0.003
	Unilateral	25 (10.97)	13 (52)	12 (48)		
Degree of consanguinity**	None	46 (20.18)	0	46 (20.18)	0.000*	0.000
	Cousins	127 (50.70)	127 (50.70)	0		
	Relatives	54 (29.83)	54 (29.83)	0		

The total number of the patients included in this study is 228.
* P-value < 0.05 was considered significant.
** The total number of these two features is 227 patients, one patient had a missing data.

has a statistically non-significant association with neither laterality of eye involvement nor parents' consanguinity. Rana and Saba from Pakistan have also shown that males with congenital paediatric cataract outweigh the number of females. However, Alcalde from Spain in 2021 has contradicted this result by stating that 64.5% of patients with paediatric cataract were female.[8, 23-24] Variability of gender effect on congenital paediatric cataract might be due to the type of genetic inheritance among different races.

CONCLUSION

Parental consanguinity is found in most patients with paediatric cataracts, suggesting that the inheritance of this disease in Iraq is probably autosomal recessive. There was a statistically significant association between having bilateral cataract and a positive family history of paediatric cataract with parental consanguinity. A paediatric cataract is more common in males than in females though this difference is statistically non-significant. Most cases were presented below the age of one year, and the rate is decreasing progressively with increasing age.

REFERENCES

1. Garg A, and Rosen E. Instant clinical diagnosis in ophthalmology, Strabismus. Jaypee Brothers Medical Publishers Pte Ltd, 2011.
2. Louis B. Cantor, Christopher J. Rapuano, George A. Cioffi. Basic and Clinical Sciences Course, Section 6: Pediatric ophthalmology and strabismus. American Academy of Ophthalmology, San Francisco 2016. Available from: https://www.aao.org/assets/5e0f04a7-77a1-457b-81af-2f650333faae/636312517616000000/bcsc1718-s06-pdf.
3. Mansouri B, Stacy RC, Kruger J and Cestari DM. Deprivation Amblyopia and Congenital Hereditary Cataract. *Seminars in Ophthalmology*, 2013;28:5-6, 321-326. doi:10.3109/08820538.2013.825289
4. Kanski JJ, and Bowling. Kanski clinical ophthalmology: a systematic approach. Elsevier Health Science; 2011.
5. Wolff E, Bron AJ; Tripathi RC, Tripathi BJ. Wolff's Anatomy of the Eye and Orbit. 8th Ed. London; Weinheim; Tokyo: Chapman & Hall Medical, 1997.
6. Pichi F, Lembo A, Serafino M, Nucci P. Genetics of Congenital Cataract. *Dev Ophthalmol*. 2016;57:1-14. DOI: 10.1159/000442495. Epub 2016 Apr 1. PMID: 27043388.
7. Chan WH, Biswas S, Ashworth JL, Lloyd IC. Congenital and infantile cataract: aetiology and management. *Eur J Pediatr*. 2012 Apr;171(4):625-30. doi:10.1007/s00431-012-1700-1. Epub 2012 Mar 1. PMID: 22383071.
8. Moseley M, Fielder AR, editors. Amblyopia: a multidisciplinary approach. Elsevier Health Sciences; 2002.
9. Antonio-Santos A, Vedula SS, Hatt SR, Powell C. Occlusion for stimulus deprivation amblyopia. *Cochrane Database of Systematic Reviews* 2020 Mar 23;3(3):CD005136. DOI: 10.1002/14651858.CD005136.pub4.
10. Singh J. The portal for rare diseases and orphan drugs. *J Pharmacol Pharmacother* 2013;4(2):168-9.
11. Yanoff M and Duker JS. Ophthalmology. 3rd ed. Mosby; 2008.
12. Hamamy H. Consanguineous marriages : Preconception con-

sultation in primary health care settings. *J Community Genet*. 2012;3(3):185-192. doi:10.1007/s12687-011-0072-y.

13. Tadmouri GO, Nair P, Obeid T, Al Ali MT, Al Khaja N, Hamamy HA. Consanguinity and reproductive health among Arabs. *Reprod Health*. 2009 Oct 8;6:17. doi: 10.1186/1742-4755-6-17. PMID: 19811666; PMCID: PMC2765422.
14. Lafta FM. Consanguineous Marriages and Some Reproductive Health Parameters for Sample from Families in Baghdad, Iraq. *AL-Mustansiriya J Sci*. 2010;21(5):345-54. doi: 10.5958/0976-5506.2019.01069.6.
15. Bittles AH. Endogamy, consanguinity and community genetics. *J Genet*. 2002 Dec;81(3):91-8. doi:10.1007/BF02715905. PMID: 12717037.
16. American Academy of Ophthalmology. Pediatric Cataract - Asia Pacific [Internet]. 2016 [cite 7 January 2022]. Available: https://www.aao.org/topic-detail/pediatric-cataract-asia-pacific-2#disqus_thread.
17. Wilson ME, Trivedi RH, Pandey SK, editors. Pediatric cataract surgery: techniques, complications, and management. Lippincott Williams & Wilkins; 2005. Available from: https://books.google.iq/books/about/Pediatric_Cataract_Surgery.html?id=gLJZDD2igCMC&printsec=frontcover&source=kp_read_button&redir_esc=y#v=onepage&q&f=false.
18. Khan L, Shaheen N, Hanif Q, Fahad S and Usman M. Genetics of congenital cataract, its diagnosis and therapeutics, *Egyptian Journal of Basic and Applied Sciences* 2018;5:4,252-257. doi: 10.1016/j.ejbas.2018.07.001.
19. Khokhar SK, Dhull C, editors. Atlas of Pediatric Cataract. Springer Singapore; 2019.
20. Elkington AR, Frank HJ. Clinical optics. Blackwell Publishing.
21. Denniston A, Murray P, editors. Oxford handbook of ophthalmology. OUP Oxford, 2014.
22. Rana AM, Raza A, Akhter W. Congenital Cataracts; Its Laterality and Association with Consanguinity. *Pakistan Journal of Ophthalmology*. 2014 Dec 31;30(4). Available from: http://www.pjo.com.pk/30/4/2%20OA%20Afia%20Matloob.pdf.
23. Saba and S. Irshad. Etiology and Association of Congenital / Acquired Cataract, with Other Ocular Anomalies in Pakistani Population. Pakistan J. Zool 2012;54(3):1001-1500. doi: https://dx.doi.org/10.17582/journal.pjz/20200921070958.
24. Fernández-Alcalde C, Nieves-Moreno M, Noval S, Peralta JM, Montaño VEF, del Pozo Á, et al. Molecular and Genetic Mechanism of Non-Syndromic Congenital Cataracts. Mutation Screening in Spanish Families. *Genes* 2021;12(4):580. doi: https://doi.org/10.3390/genes12040580.

Abbreviations list: Catalogue of transmission of genetics in the Arab population (**CTGA**), Inbreeding coefficient (**F**), Statistical Package for Social Science (**SPSS**), United States of America (**USA**), Toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus (**TORCH**), Venereal disease research laboratory (**VDRL**).

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