FP190

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Prognostic significance of *CYP1B1* variants in childhood glaucoma

INTRODUCTION

Glaucoma in children is a potentially blinding disease and poses difficult clinical challenges in both diagnosis and management. The CGRN[1] has a universally accepted system of classification of childhood glaucoma. Patients with isolated trabeculodysgenesis are deemed to have ‘‘primary glaucoma,’’ which could be primary congenital glaucoma (PCG) or juvenile open angle glaucoma (JOAG).

PCG is most common form of congenital glaucoma, manifest, most commonly, as anterior segment dysgenesis (ASD). Childhood glaucoma is highly variable groups of conditions. The presentation, Onset, severity, symptoms can be highly variable. Even the outcome if variable. Children with similar presentation and profile have different, sometimes even contrasting outcome. Even with same surgeon and same surgery, the outcome can be highly variable.[2]

Very often there is phenotype generalization of childhood glaucoma patients. Most of the previous reports described all children with buphthalmos, hazy cornea and raised IOP as “PCG”. However, we are not sure whether the genetic variants actually represent PCG or other non-acquired ocular anomalies. A distinct entity was noted amongst the children previously diagnosed as PCG. These children had intractable glaucoma and required multiple surgeries for IOP control and also had persistent corneal scarring. Twelve of 13 patients harboured *CYP1B1* variants. Genetic study for twelve children was done. Nine of these 12 patients (83.3%) were homozygous for [c.1169G > A(p.Arg390His)] in Exon-3 of *CYP1B1* and they were diagnosed as neonatal onset congenital ectropion uveae (NO- CEU). [3]

CYP1B1 has been identified as the leading cause of PCG. More than 150 mutations in *CYP1B1* have been associated with PCG [4]. *CYP1B1* (OMIM# 601771) is a member of the

cytochrome P450 superfamily and encodes a monooxygenase involved in the metabolism of a broad range of endogenous and exogenous substrates. Mutations in *CYP1B1* have been shown to cause various glaucoma phenotypes. Multiple studies have studied role of *CYP1B1* mutation in development of childhood glaucoma but none of the studies have discussed role of various variants seen in patients with CYP1B1 mutations. In this study we aimed at studying different *CYP1B1* genetic variants found in a cohort of children with non-acquired glaucoma (NAG) and also to analyze their correlation with the phenotype and outcome.

METHODOLOGY

The study was a prospective cohort study conducted in tertiary care hospital in north India located in the state of Punjab. Children who presented with newly diagnosed NAG between January 2021 and January 2023 underwent targeted gene capture sequenced on a Illumina sequencing platform (CES). Sequences were aligned to the human reference genome (GRCh38.p13). The pathogenicity of variants was determined using ACMG guidelines and targeted variant analysis was done by PCR and Sanger sequencing. Children harbouring *CYP1B1* variants and completing a minimum 6-month postoperative follow-up were included. We correlated the genetic variants to the phenotype and outcome.

RESULTS

During the study duration a total of 175 children with non-acquired glaucoma (NAG) with ocular anomalies underwent Clinical Exome Sequencing (CES). Based on clinical diagnosis. Major chunk of the cohort were primary congenital patients. About 41% children were diagnosed as PCG followed by CEU (26%). Axenfeld reiger syndrome/anomaly were 11%. Aniridia , peters anomaly, sturge weber syndrome or other phacomatosis constituted minor percentage [Figure 1].

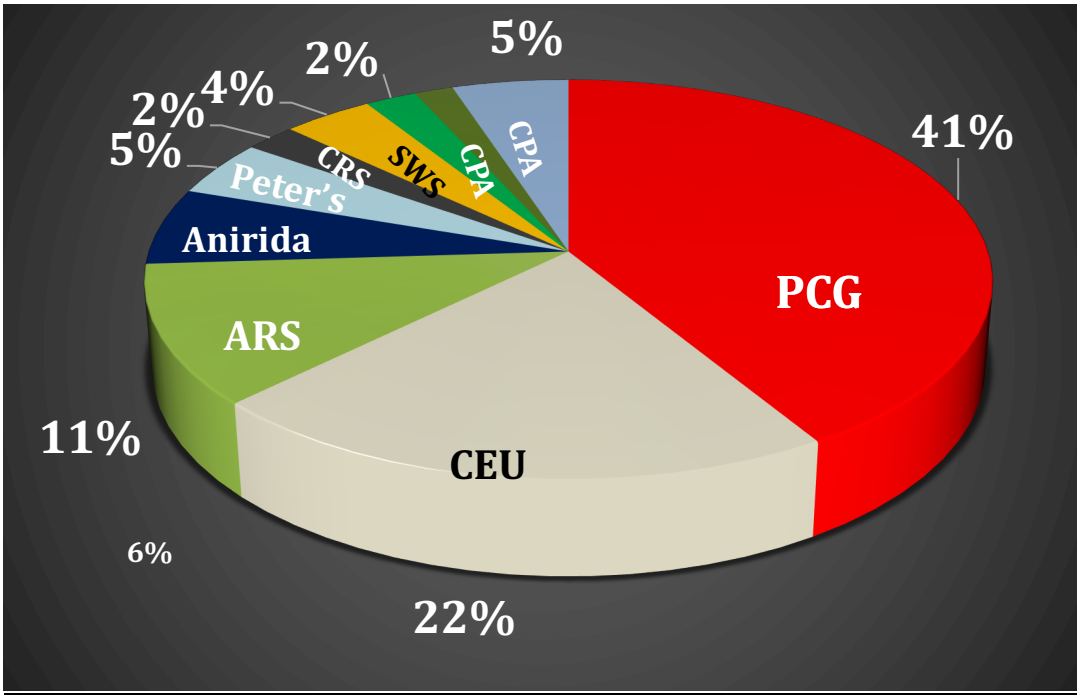

Figure 1 – Diagnosis wise distribution of Non acquired glaucoma (NAG) children

126 (72.0%) harboured genetic variants, of which 98 (77.8%) matched the phenotype; classified as pathogenic. Of these pathogenic variants, the most common genetic mutation seen was in *CYP1B1*. About 52 (41.3%) patients had mutation in *CYP1B1* gene followed by PAX6 and FOXC1. Other minor percentage was seen with mutations in *LTBP2, FOXE3,* and *PITX2* genes. About 28% patients had unique mutations whereas equal percentages of patients were found to have no mutation on genetic study [Figure 2].

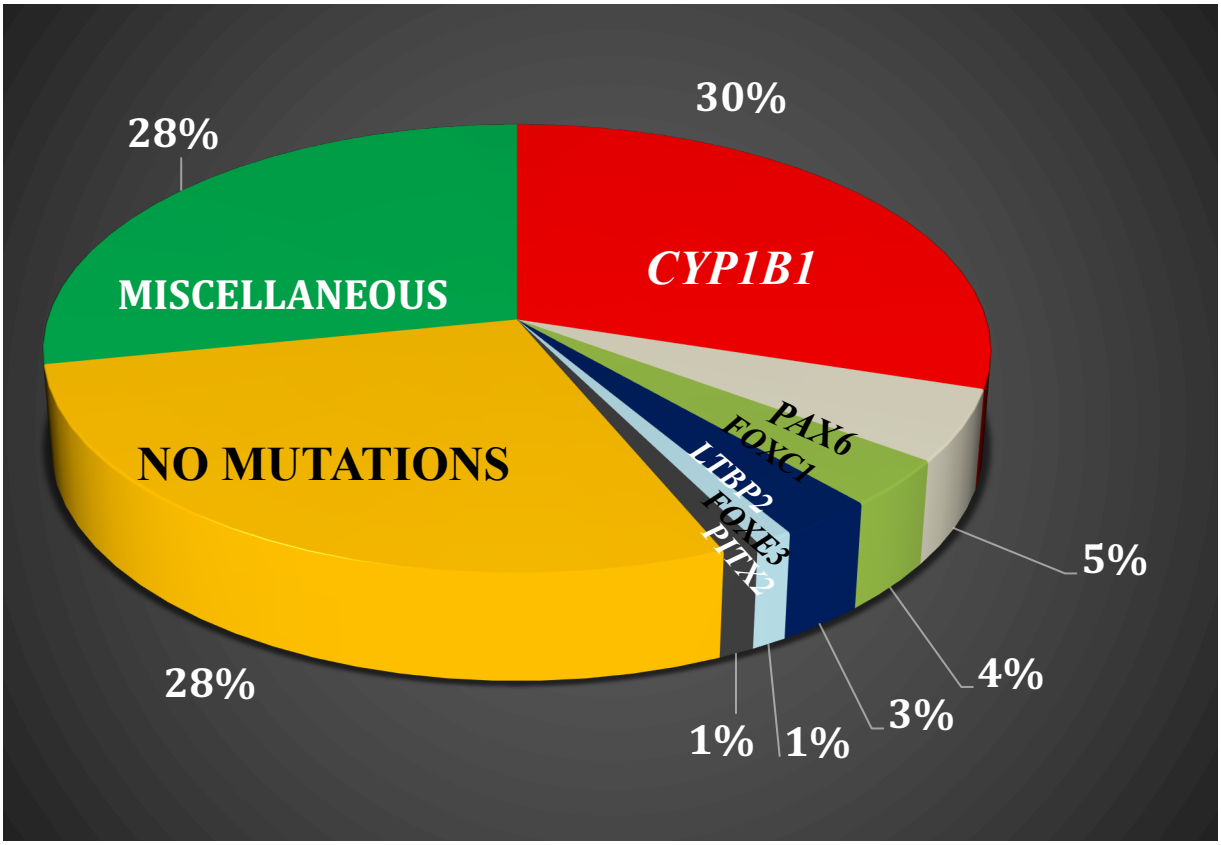

Figure 2 – Genetic mutation wise distribution of Non acquired glaucoma (NAG) children

Of the 52 patients with *CYP1B1* mutation, 34(65.38%) had the c.1169G>A (p.Arg390His) variant; All 25 children with homozygous c.1169G>A (p.Arg390His) variants and five with compound heterozygous variants had a common phenotype: neonatal-onset congenital ectropion uveae (NO-CEU), with a scarred cornea suggestive of *CYP1B1* keratopathy. 11/52(21.15%) children harboured the c.1103G>A (p.Arg368His) variant and they had better corneal clarity at presentation and showed favourable outcomes. The remaining children had mixed variants with no definite phenotype or consistent outcomes.

About 78.1% eyes with *CYP1B1 with* c.1169G>A(p.Arg390His) variant had poor surgical outcome. The outcome was worst in homozygous state. Eyes with *CYP1B1* mutation with c.1103G>A (p.Arg368His) has better outcome with about 75% of them

having favourable. Other homozygous or heterozygous variants of *CYP1B1* mutation has non specific outcome.

CONCLUSION

Our study identified one uniformly poor prognosis variant i.e c.1169G>A(p.Arg390His) and one variant that potentially indicates a favourable prognosis which was c.1103G>A (p.Arg368His). These findings provide valuable insights into the prognostic significance of *CYP1B1* variants and highlight the potential of CES as a diagnostic tool for childhood glaucoma.

REFERENCES

1. Beck AD, Chang TCP, Freedman SF. Definition, classification, differential diagnosis. In: Childhood Glaucoma: Consensus Series 9. Amsterdam: Kugler; 2013.

2. Kaushik S, Dhingra D, Vibha B, Saini A, Gupta G, Snehi S, Singh N, Thattaruthody F, Pandav SS. Neonatal-onset congenital ectropion uveae: a distinct phenotype of newborn glaucoma. American Journal of Ophthalmology. 2021 Mar 1;223:83-90.

3. Kaushik S, Choudhary S, Kaur A, Srivastava P, Pokharel B, Akella M, Pandav SS. Neonatal-Onset Congenital Ectropion Uveae May Be Caused by a Distinct CYP1B1 Pathologic Variant. American Journal of Ophthalmology. 2022 Jul 1;239:54-65.

4 Chouiter L, Nadifi S. Analysis of CYP1B1 Gene Mutations in Patients with Primary Congenital Glaucoma. J Pediatr Genet. 2017; 6: 205-14.