

Review Article

Eradicating primary congenital glaucoma from Saudi Arabia: The case for a national screening program



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Abstract

The prevalence of primary congenital glaucoma (PCG) in Saudi Arabia is high and the condition is a cause of childhood blindness in the country. Children often present with severe disease, requiring multiple procedures and a lifetime of medical care. The social and economic burden of the condition is substantial. Presently, the mainstay of management is early diagnosis and treatment of PCG. Premarital screening, especially in recessive diseases, such as PCG can be immensely useful by detecting the presence of a defect in the causative gene, followed by genetic counseling to potential couples that will lead to eradication of the disease in future generations. The introduction of a national screening program similar to the one already functioning for thalassemia, could potentially eliminate childhood blindness from PCG in Saudi Arabia and is likely to prove cost-effective.

Keywords: Primary congenital glaucoma, Genetic screening, Childhood blindness, Disease prevention

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Introduction

Primary congenital glaucoma (PCG) is usually a severe form of glaucoma characterized by raised intraocular pressure from birth, in the absence of other specific ocular or systemic conditions that can cause glaucoma. In Saudi Arabia PCG is estimated to have a prevalence of up to 10 times higher than in the West.¹ In 2014, around 251,736 live births were reported in Saudi Arabia.² Based on the incidence of 1 in 2500 to 3000 live births of PCG,³ there may be up to 100 newborns with PCG every year in the Saudi population. At King Khaled Eye Specialist Hospital (KKESH, a tertiary referral

hospital for eye diseases throughout the kingdom of Saudi Arabia) between 60 and 90 children with newly diagnosed PCG have been seen annually consistently for the last 15 years and more recently documented in the registry at average of 70 cases per year. It is likely that the numbers of PCG cases in the Kingdom are increasing, as over the last decade, several University, Ministry of Health and private hospitals are providing care to these children in addition to KKESH.

The phenotype of PCG seen in Saudi Arabia is typically more severe than that reported in the West.^{3,4} The severe phenotype is characterized by 83% with bilateral disease, a

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quarter of who have moderate or severe corneal haze at first presentation, many with features of anterior segment dysgenesis.³ PCG is a leading cause of childhood blindness in the Kingdom, with around 20% of childhood blindness attributable to the condition.^{5,6} As nearly 6.5 million of the Saudi population are below the age of 15 years and projected to increase in the next decade,² the implications for future nationwide blindness related to diseases such as PCG are significant.

The burden of PCG in Saudi Arabia

At an individual level, a diagnosis of PCG inevitably commits a child to numerous hospital visits following diagnosis, and the children are often subjected to multiple surgical procedures to control the intraocular pressure.⁷ Despite this, the visual prognosis is often poor, with nearly a third of patients having severe visual loss.⁷ The condition carries a reduced quality of life⁸ and significant psychological disability and burden for caregivers.⁹

Why screen for PCG in Saudi Arabia?

Presently, the mainstay of control of PCG is emphasis on early detection and treatment. However, in an age where genetic screening is widely available for other diseases, one could easily argue a case for prevention of PCG in Saudi Arabia. Nearly 90% of the PCG in Saudi Arabia is hereditary, with autosomal recessive inheritance and high penetrance.¹⁰ In practice, this means that the majority of new cases occur when both parents are often unaffected and carry an altered copy of the affected allele, particularly in consanguineous marriages. The prevalence of autosomal recessive disease, such as PCG, is very high in societies where consanguinity rate is high: in Saudi society the consanguinity rate can reach up to 65% in some parts of the kingdom.¹¹ Regional consanguinity rates have been reported to be between 25% and 30% of all marriages.¹²

In terms of genetics, mutations in cytochrome P450, family 1, subfamily B, polypeptide 1 (*CYP1B1*) have been identified in up to 86% of tested Saudi patients with PCG and thus establishing the *CYP1B1* gene-mutations as the major cause of PCG in Saudi Arabia.^{1,10} The mutation positive rate obtained among Saudi PCG patients (75.9–86%) is the highest reported thus far globally.⁹ Furthermore, four mutations in the *CYP1B1* gene are known to account for up to 90% of cases which allows for creation of a cost-effective gene screening panel (local cost for testing would be approximately \$80 per individual).

Is screening for PCG practical?

Genetic screening programs for other conditions have proved successful in Saudi Arabia. Premarital screening and genetic counseling in the Kingdom have markedly reduced the number of at-risk marriages for hemoglobinopathies.¹³ Couples are screened before marriage and this gives them the chance to choose a low-risk marriage partner. The cost of screening an individual under this program has not been reported. Under the Saudi Premarital and Screening Genetic program, couples with marriage proposals report to the nearest healthcare clinic where the program staff collects

basic demographic information and a blood sample. Blood samples were then tested for sickle cell disease and β -thalassemia using hemoglobin electrophoresis. Depending on the blood test results, couples are then issued with pre-marriage compatibility certificates. Couples are deemed to be 'high-risk' if both have the disease or carry the abnormal gene and are given appropriate genetic counseling.

How would screening for PCG work?

We propose a similar national genetic screening program for PCG in Saudi Arabia, with the long-term goal toward eradicating PCG in Saudi Arabia. We envision this program having two arms that targets affected and non affected individuals. The first arm, would offer genetic pre-marital counseling for individuals at high-risk of having a child with PCG. 'High-risk' in this context includes unmarried individuals already affected by the condition and individuals known to be potential carriers of the *CYP1B1* mutation (i.e. siblings of affected individuals). Population surveys suggest that pre-marital counseling can successfully alter an individual's choice of spouse after counseling.¹¹ An existing web-based registry of affected individuals at KKESH, may also be used to identify many of the high-risk individuals.¹⁴ The second arm could either mirror and piggy back on to the National Program for screening of hemoglobinopathies or be focused to screen unaffected individuals pre-maritally in areas of the country with the largest number of patients with PCG.³

Would screening be cost-effective?

A national genetic screening program would require national funding from the Ministry of Health. The cost is likely to compare favorably against the cost of caring for children with newly diagnosed PCG in the Kingdom of Saudi Arabia. The annual cost of care for childhood glaucoma in the West was reported to be in excess of \$20,000 USD per year per case¹⁵; in the Kingdom the annual costs of care is roughly calculated to be 20,000–23,000 USD per year per case. The cost included surgery/consumables, hospitalization, examination under sedation/anesthesia in the post-operative period, medication and travel of parent and child. These elevated costs are likely due to the severity of the phenotype,³ likelihood of more surgical interventions and associated transportation costs for families seeking care for these children.

We constructed a simple economic cost model, to estimate the economic gain of screening for PCG in Saudi Arabia based on screening 160,000 couples who get married annually.² Couples who are found to have the candidate gene would then referred for genetic counseling. A SNP-specific assay, can detect the 4 most common mutations in the *CYP1B1* gene (responsible for >90%) of the PCG cases. Based on this simple economic cost model we estimate that this method of screening would be at least twice as cost-effective per case per year than treating children for PCG (based on each child using just one glaucoma medication during their lifetime and undergoing one surgical procedure). The usual treatment regimen for a child with PCG in Saudi Arabia involves more than one medication and 2–3 surgical procedures. Therefore, the screening and counseling program we propose would likely be even more cost-effective than our current estimate.

Conclusions

Prevention of childhood blindness, due to the number of years of future disability, is a priority for the World Health Organization.¹⁶ Accordingly, Saudi Arabia needs to tackle PCG, which due to its genetic characteristics is largely preventable. With the institution of a relatively simple screening and counseling program in the Kingdom, a major cause of childhood blindness with its associated societal burden can be alleviated and the dream of eradicating blindness from PCG in the country can be realized.

Conflict of interest

The authors declare that there is no conflict of interest.

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