Determinants of severity at presentation among young patients with early onset glaucoma

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Aim: The aim of this study was to evaluate the clinical, socio-economic, and demographic factors associated with the severity at presentation among juvenile primary open angle glaucoma (JOAG) patients. Materials and Methods: Age at diagnosis, family history, baseline intraocular pressure (IOP), access to health-care, socio-economic status, and glaucoma awareness among 80 unrelated JOAG patients presenting between 10 years and 40 years of age were analyzed for their association with the severity at presentation. Severity at presentation was graded based on worse eye visual field using the advanced glaucoma intervention study score and on binocular visual field defects at presentation. Results: Patients with a positive family history presented 4 years earlier (P = 0.045, confidence interval [CI]: 0.09-8.8) compared to those without a family history. Lower socio-economic status (Odds ratio [OR] 5.7, P = 0.01, CI: 1.5-22), and higher baseline IOP (OR 7, P = 0.003, CI: 1.9-26) were associated with severe glaucomatous visual field defect at presentation. A negative family history was associated with a 10 times likelihood of presenting with a severe glaucomatous field defect (OR 0.1, P = 0.007, CI: 0-0.5). Conclusions: Clinical, socio-economic, and demographic factors are contributory to the severity at presentation among young patients with early onset glaucoma. Presence of a family history is associated with an earlier presentation among these patients and a reduced risk of the severe presentation.

Key words: Glaucoma severity, juvenile glaucoma, juvenile-onset primary open angle glaucoma, visual field defects

Juvenile-onset primary open angle glaucoma (JOAG) is an uncommon disorder that has been traditionally classified as glaucoma affecting the age group between 10 years and 40 years. It is known to have an autosomal dominant pattern of inheritance. Clinically, JOAG is associated with myopia, high intraocular pressure (IOP), advanced glaucomatous optic neuropathy, and severe visual field defects (VFD).

There is substantial variability in the presentation of the disease. On one hand, JOAG patients may present with high IOP and bilateral diffuse VFD while on the other hand, some present with mildly raised IOP and minimal VFD or may even present as unilateral glaucomatous optic neuropathy. Because of the considerable phenotypic variability of the disease it is necessary to understand why some patients present with more severe, while others with a less severe disease. Among patients from the lower socio-economic strata, the problem may be compounded by lack of awareness regarding the disease, lack of education or poor access to healthcare services ultimately leading to late presentation. Most studies associated with severity at presentation of glaucoma deal with socio demographic factors alone while it is known that clinical, and even genetic factors may be crucial determinants of severity at presentation especially, in those with early onset of glaucoma. Furthermore, most such studies focus on glaucoma patients in the adult age group. In this study, we aimed to look into the socio demographic and the clinical factors associated with the disease severity at presentation among young patients with JOAG.

Materials and Methods

The study included 80 unrelated JOAG patients presenting in the glaucoma clinic at our tertiary eye care center from 2005 to 2010. The study was approved by the Ethics Committee of our Institute. An informed consent to participate in the study was obtained from all patients and from parents when the patients were <18 years of age and the study conformed to the tenets of the Declaration of Helsinki.

Following were considered as the diagnostic criteria for JOAG
1. Primary open angle glaucoma (POAG) patients presenting between 10 years and 40 years of age
2. IOP >22 mmHg in at least one eye on more than two occasions
3. Glaucomatous optic neuropathy in one or both eyes with visual field loss consistent with optic nerve damage
4. Open angles on gonioscopy in both eyes.

Exclusion criteria were: History of corticosteroid use, presence of any other retinal or neurological pathology, evidence of secondary causes of raised IOP (pigment dispersion, pseudoxfetion or trauma), those with any pathology detected on gonioscopy such as angle recession, pigmentation of the angle greater than grade 3 or peripheral anterior synechia, those with corneal diameter >12 mm and those who had any ocular surgery or laser trabeculoplasty in the past.

JOAG patients were administered a questionnaire and details pertaining to their socio-economic and demographic
status were obtained. The information as provided by the parents was relied upon for those <18 years. Among the clinical attributes as ascertained from their records, age at diagnosis, gender, presence of a family history, baseline IOP, and the visual field defect at presentation were assessed. A family history of glaucoma was considered to be present if 2 or more first degree relatives were affected including the proband.

Following socio-economic and demographic parameters were assessed to look for an association with the severity at presentation.

**Socio-economic status**
The patients were classified into different socio-economic classes (SEC) depending upon their urban or rural background respectively. Scoring was based on the total family income, educational level, per capita income, occupation of the head of a family member that has been described, and validated previously in population studies.8

**Educational level**
Depending upon their educational level, the patients were classified as:
I. Illiterate
II. ≤Matriculate
III. High School
IV. Graduate/Post-graduate

**Glaucoma awareness**
General awareness regarding glaucoma among patients was assessed using the following broad questions:
i. If they had previously heard of glaucoma
ii. If they were aware of disease symptomatology
iii. If they were aware of glaucoma running in families
iv. If they knew about the role of intra ocular pressure in causing glaucoma
v. If the visual loss due to glaucoma is irreversible or not
vi. If they were aware of any treatment modalities available for glaucoma.

Awareness was accordingly classified as either complete or incomplete depending upon the responses of the patients. Upon answering each of the questions correctly, the awareness was classified as complete, and otherwise incomplete.

**Health care accessibility**
Assessment of accessibility to an ophthalmologist was carried out by enquiring about the distance (in kilometers) from the nearest ophthalmologist, availability of easy transport, and history of prior consultation with an ophthalmologist.

Easy availability of transport was assessed on subjective response of the patients. All patients with a private transport were classified under easy availability whereas, those using public transport were further enquired about the time and expenditure involved in arranging transport and were then classified upon their subjective ease in getting health-care access. No objective criteria were used.

**Grading severity of glaucoma**
Severity of the disease was graded on the visual field score using the 30-2 visual fields of the Humphrey visual field analyzer of the worse eye. On the basis of advanced glaucoma intervention study scoring system, patients presenting with a worse eye scores greater than 12 were classified as severe disease whereas, those with scores less than 12 as non-severe.7

Any patient with vision <3/60 in one eye was classified as severe glaucoma. In patients with a unilateral glaucomatous optic neuropathy, the worst eye was considered for analysis.

Binocular VFD was also used to grade binocular severity. These were graded as:9
a. Mild: <½ visual field loss in one eye
b. Moderate: >½ visual field loss in one eye or <½ visual field loss in both eyes
c. Severe: >½ visual field defect in both eyes or complete visual field loss in one eye.

**Statistical analysis**
Statistical analysis was carried out to study the association of various socio-economic and clinical attributes with disease severity using SPSS version 16.5 (Chicago IL, USA). A descriptive analysis of the entire cohort was carried out, and data were represented as means and frequency percentages. Chi-square test and an independent ‘t’-test were applied to compare categorical and continuous data respectively. Odds ratio was calculated with 95% confidence interval. A univariate and then multivariate binomial logistic regression analysis of the factors associated with severity at presentation was performed. The disease severity at presentation using a worse eye VFD and with binocular field defects at presentation was analyzed separately. A ‘P’ ≤ 0.05 was considered significant.

**Results**

**Clinical features**
The mean age at diagnosis of patients was 25.4 ± 8.7 years with an equal distribution of patients in the age groups of 10-20 years (32%), 21-30 years (34%) and 31-40 years (34%). Mean age at presentation among females was 21 ± 10 years compared to males 26 ± 8.25 years; P = 0.045.65 (81%) patients were male.

No, statistically significant difference was found in the age at diagnosis and severity of visual field defect. The mean age at diagnosis was 25 ± 8.7 years and 25.9 ± 8.9 years among patients with and without severe visual field defect at presentation (P = 0.644).

A positive family history for glaucoma was elicited in 21 patients (25%). Patients with a positive family history presented 4 years earlier (P = 0.045, CI: 0.09-8.8) compared to those without a family history. No statistically significant difference was found in the worse eye mean deviation scores or the highest untreated (baseline) IOP among patients with or without a family history of glaucoma [Table 1]. However, considering the binocular VFD it was found that those with a positive family history were 10 times less likely to present with severe binocular VFD [Table 2].

The mean highest untreated IOP at presentation among our JOAG patients was 39 ± 8 mmHg. Fig. 1 shows the distribution of patients with regard to the highest untreated IOP at presentation.

**Socio-economic and demographic features**
Socio-economic evaluation revealed 44 (55%) patients belonged to upper and upper middle classes and 36 (45%) to the lower
significant association between gender and glaucoma awareness was found in the study ($P = 0.346, CI: 0.43-10.43$).

Most of the patients in our study had no difficulty in accessing health-care facilities with more than two-third of patients having an easy access to an ophthalmologist.

Forty three (54%) patients in our study presented with a severe visual field defect. Using the binocular VFD for grading severity of glaucoma, 53% of the JOAG patients had severe VFD, 10% had moderate field defects and 37% had mild defect.

Table 1: Association of family history of glaucoma with age at diagnosis, gender and severity of visual field defect in the worse eye

| Factors                  | Family history | $P$ value |
|--------------------------|----------------|----------|
|                          | Positive N=21  | Negative N=59 |
| Gender (%)               |                |          |
| Male                     | 16 (76.2)      | 49 (83.1) |
| Female                   | 05 (23.8)      | 10 (16.9) |
| Mean age (±SD) years     | 22.14±7.6      | 26.59±8.9 |
| Worse MD score (dB)      | -18.07±10.44   | -20.8±13.16 |

SD: Standard deviation, MD: Mean deviation

Figure 1: Distribution of patients with regard to baseline intraocular pressure

Table 2: Socio-economic and clinical correlates with severity of disease based on advanced glaucoma intervention study scores in the worse eye

| Factors          | AGIS scores | Univariate model unadjusted | Multivariate model adjusted |
|------------------|-------------|-----------------------------|-----------------------------|
|                  | >12 N=43    | $P$ value odds ratio        | $P$ value odds ratio        |
| Gender           |             |                            |                            |
| Female           | 5 (11.6)    | 10 (27)                    |                            |
| Male             | 38 (88.4)   | 27 (73)                    |                            |
| Family history   |             |                            |                            |
| Negative         | 34 (79.1)   | 25 (67.6)                  |                            |
| Positive         | 9 (20.9)    | 12 (32.4)                  |                            |
| IOP              |             |                            |                            |
| ≤35 mmHg         | 14 (32.6)   | 24 (64.9)                  |                            |
| >35 mm Hg        | 29 (67.4)   | 13 (35.1)                  |                            |
| SEC              |             |                            |                            |
| Upper            | 18 (41.9)   | 26 (70.3)                  |                            |
| Lower            | 25 (58.1)   | 11 (29.7)                  |                            |
| Education        |             |                            |                            |
| ≤ Matriculation  | 26 (60.5)   | 14 (37.8)                  |                            |
| >Matriculation   | 17 (39.5)   | 23 (62.2)                  |                            |
| Awareness        |             |                            |                            |
| Complete         | 11 (25.6)   | 7 (18.9)                   |                            |
| Incomplete       | 32 (74.4)   | 30 (81.1)                  |                            |
| Accessibility    |             |                            |                            |
| Yes              | 27 (62.8)   | 25 (67.6)                  |                            |
| No               | 16 (37.2)   | 12 (32.4)                  |                            |

SEC: Socio-economic classes, CI: Confidence interval
There was no correlation between the age at diagnosis with the severity of VFD ($r = 0.23; P = 0.4$). JOAG patients presenting at a younger age were as much likely to have a severe disease as those presenting later [Fig. 2].

Patients were categorized into those with highest untreated IOP >35 mmHg and ≤35 mmHg. A univariate binary logistic regression analysis showed a statistically significant association between the highest untreated IOP of >35 mmHg, lower socio-economic status and educational level below matriculation among JOAG patients with a worse eye VFD scores. Using a multivariate analysis only baseline untreated IOP >35 mmHg was found to be most significantly associated with severe disease at presentation; adjusted odds ratio (AOR): 3.8, $P = 0.022$ [Table 3].

Table 3 highlights the association of various factors with the disease severity based on the binocular VFD. Analysis revealed 7 times and approximately 6 times higher likelihood of presenting with binocularly severe VFD among those with baseline IOP >35 mmHg (AOR: 7 $P = 0.003$) and lower SEC respectively (AOR: 5.7 $P = 0.01$).

**Discussion**

Patients of JOAG are known to present with high IOP and severe glaucomatous damage at presentation compared to adult POAG patients. However even among JOAG patients the severity at presentation may vary. Factors associated with severity at presentation among adult glaucoma patients include the lower socio-economic status, presence of a family history, poor health literacy and ethnicity.[9-11] Unfortunately, there are no studies among young patients with early onset glaucoma that have looked into the factors associated with severity at presentation. Apart from a higher baseline IOP our study confirmed that poor socio-economic status was associated with the greater disease severity at presentation among JOAG patients.

JOAG patients in our study with a family history of glaucoma tended to present earlier and thus had less severe disease, probably because they were detected earlier. This is supported by Landers et al.[12] who also found positive family history to be associated with better visual fields when

| Table 3: Socio-economic and clinical correlates with severity of disease based on binocular visual field defects |
| --- |
| **Factors** | **Visual field defect** | **Univariate model unadjusted** | **Multivariate model adjusted** |
|  | Severe N=43 | Non-severe N=37 | 'P' value OR | 'P' value OR |
| Gender | | | | |
| Female | 4 (9.3) | 11 (29.7) | 14.1 (1.1-14.3) | 0.026 |
| Male | 39 (90.7) | 26 (70.3) | - | - |
| Family history | | | | |
| Negative | 36 (83.7) | 23 (62.2) | 0.3 (0.1-0.9) | 0.033 |
| Positive | 7 (16.3) | 14 (37.8) | 0.1 (0-0.5) | 0.007 |
| IOP | | | | |
| ≤35 mmHg | 12 (27.9) | 26 (70.3) | 16.45 (2.3-17.3) | 0.000 |
| >35 mmHg | 31 (72.1) | 11 (29.7) | 17 (1.9-26) | 0.003 |
| SEC | | | | |
| Upper | 18 (41.9) | 26 (70.3) | 14.1 (1.4-11.7) | 0.009 |
| Lower | 25 (58.1) | 11 (29.7) | 15.7 (1.5-22) | 0.01 |
| Education | | | | |
| ≤matriculation | 28 (65.1) | 12 (32.4) | 12.5 (0.1-0.8) | 0.002 |
| >matriculation | 15 (34.9) | 25 (67.6) | - | - |
| Awareness | | | | |
| Complete | 10 (23.3) | 8 (21.6) | 1.11 (0.3-4.0) | 0.871 |
| Incomplete | 33 (76.7) | 29 (78.4) | - | - |
| Accessibility | | | | |
| Yes | 25 (58.1) | 27 (73) | 11.81 (0.6-4.9) | 0.245 |
| No | 18 (41.9) | 10 (23) | - | - |

SEC: Socio-economic classes, CI: Confidence interval, OR: Odds ratio
patients under 50 years of age were considered. Other studies however, found the presence of a positive family history as a significant risk factor for severity among POAG patients.\textsuperscript{[10-13]} Juvenile glaucoma patients with a positive family history in our study were 10 times less likely to have severe binocular VFD at presentation. Probably affection of one of the eyes and awareness regarding disease among those with a positive family history could be the contributory factors to their seeking care and early detection. Patients with a family history of glaucoma are more aware of the disease,\textsuperscript{[10]} and increasing awareness among the family members of patients could be responsible for earlier presentation.\textsuperscript{[10,17]} In our study too, JOAG patients with a positive family history tended to present at least 4 years earlier compared to those who did not have a family history of glaucoma.

We found a marked lack of general awareness regarding glaucoma among the young patients. Only 22\% JOAG patients were fully aware of the disease. Lack of awareness about glaucoma across all categories of patients in India had been alluded to before though in the same study, it was found that the younger patients’ awareness was more compared to the older patients.\textsuperscript{[11]} However, in our study, we did not find an association between the awareness of the disease and the severity at presentation, which could be because most patient’s awareness was poor. Another reason could be not using a grading system for awareness in the present study and it is possible that the awareness among those with familial glaucoma may be of a higher grade compared to those without a family history.

Poor health literacy has a significant association with severe disease at presentation among glaucoma patients and also contributes to the lack of compliance to therapy.\textsuperscript{[10,18]} Glaucoma awareness has been evaluated in the past using the questionnaires that included understanding of their overall glaucoma care, medications, treatment, prevention of its consequences, and the benefits of lowering eye pressure.\textsuperscript{[19]} A study conducted in India evaluated awareness regarding glaucoma by asking questions related to the IOP, progressive nature of the disease, irreversibility of visual loss and importance of medical treatment and compliance.\textsuperscript{[11]} A similar approach was followed in the present study to evaluate awareness among patients.

Our study revealed that juvenile glaucoma patients belonging to lower SEC were 6 times more likely to present with a severe disease. A similar association of lower SEC and late presentation was evident in a previous study from India where the authors concluded that glaucoma was a disease that most severely affected the underprivileged.\textsuperscript{[11]} Socio-economic deprivation is well-known to be associated with severe disease at presentation even in developed countries.\textsuperscript{[20,21]}

More than half of the patients in our study had severe VFD at presentation. There was no association with the age at diagnosis and severity of visual field defect at presentation. Younger patients, as well as those diagnosed after 35 years were likely to present with the severe VFD. Studies have shown certain genetic mutations to be associated with younger age at diagnosis and more severe disease among early onset glaucoma patients.\textsuperscript{[22-24]} However, we believe, from our series, the influence of lower socio-economic status overwhelms most other influences on the severity of the disease though it is probable that a strong influence of certain genetic alterations may explain why some patients present with much higher IOP than other JOAG patients and this need to be further investigated.

One of the limitations of the study relates to the study being conducted at a tertiary eye care center introducing a Berksonian bias, which was evident in that majority of patients presenting to us had a severe disease. A population based study; however, is difficult due to the rarity of JOAG in the general population. Furthermore, since most JOAG patients in the study presented with advanced glaucomatous optic neuropathy in at least one eye, we were unable to evaluate severity based on the optic nerve head parameters and had to rely on VFD in grading the severity.

From the findings of the study, we can conclude that the severity of VFD among patients with early onset glaucoma, at presentation, is greater among those without a family history of glaucoma, and those from a lower socio-economic class compounded by higher baseline IOP. Thus, both clinical and socio-economic factors play a significant role in determining the severity at presentation among JOAG patients.

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