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Original Article

Incidence, Comorbidity, and Mortality of Primary Congenital Glaucoma in Korea from 2001 to 2015: A Nationwide Population-based Study

Seung Jae Lee[1,2*], Sangah Kim[3*], Tyler Hyungtaek Rim[4], Haeyong Pak[5], Dong Wook Kim[6], Jong Woon Park[1]

[1]*Department of Ophthalmology, National Health Insurance Service Ilsan Hospital, Goyang, Korea*
[2]*Department of Ophthalmology, Yonsei University College of Medicine, Seoul, Korea*
[3]*Siloam Eye Hospital, Seoul, Korea*
[4]*Singapore Eye Research Institute, Singapore National Eye Centre, Duke-NUS Medical School, Singapore*
[5]*Policy Research Affairs, National Health Insurance Service Ilsan Hospital, Goyang, Korea*
[6]*Big Data Department, National Health Insurance Service, Seoul, Korea*

Purpose: To report incidence rates of primary congenital glaucoma in Korea and evaluate comorbidity and mortality from 2001 to 2015.

Methods: This study is a nationwide and retrospective population-based study. We used claims data from the Korean National Health Insurance Service database between 2001 and 2015. Data for all patients diagnosed with primary congenital glaucoma were retrieved using the Korean Electronic Data Interchange and Korean Standard Classification of Diseases-6 codes.

Results: The number of patients with primary congenital glaucoma between 2001 and 2015 was 776, of which 437 were male (56.31%) and 339 were female (43.69%). The annual prevalence demonstrated a general decreasing trend since 2011, but this was not significant. Over the total survey period, the incidence rate was 11.0 per 100,000 births, with 12.0 cases among males and 10.0 among females. The incidence according to age was 518 (68.78%) patients at age 0, 112 (13.66%) at 1 year, 70 (8.39%) at 2 years, and 76 (9.17%) at 3 years. Of the 776 patients diagnosed with primary congenital glaucoma in the study population, 27 died. The observed mortality per 100,000 people is about 10 times higher than that of the general infant and child population under the age of 4 years. Visual impairment was the most common accompanying disability, followed by brain lesion.

Conclusions: Our study's estimates of the nationwide population-based incidence of primary congenital glaucoma in a Korean population will expand our understanding of the disease and allow healthcare systems to plan for primary congenital glaucoma.

Key Words: Age, Comorbidity, Congenital glaucoma, Incidence, Mortality

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Corresponding Author: Jong Woon Park, MD, PhD. Department of Ophthalmology, National Health Insurance Service Ilsan Hospital, 100 Ilsan-ro, Ilsandong-gu, Goyang 10444, Korea. Tel: 82-31-900-0964, Fax: 82-31-900-0049, E-mail: 2eye2@nhimc.or.kr

*These two authors contributed equally to this study.

Primary congenital glaucoma is caused by anterior segment anomaly and is characterized by increased intraocular pressure [1-3]. Most such cases of glaucoma are diagnosed before 12 months and require surgical treatment, such as goniotomy and trabeculotomy [4-6]. There is no known prevention method, and early detection is the only factor important in determining visual outcomes. Primary congenital glaucoma has been reported to occur in 2.85 of 100,000 people [7].

To date, epidemiological studies of primary congenital glaucoma have been conducted in tertiary healthcare institutions and in certain areas, but there have been no large-scale population-based studies of its incidence.

South Korea has a mandatory universal health insurance system covering the entire population of 48 million people; therefore, nearly all healthcare-related data are centralized in large databases. The Korean National Health Insurance Service (KNHIS) database includes accurate population-based incidence data for primary congenital glaucoma in Korea.

The purpose of the present study was to report the incidence, comorbidities, and mortality of primary congenital glaucoma in the entire Korean population during a 15-year period from 2001 to 2015.

Materials and Methods

Statement of ethics

This retrospective, nationwide, population-based study was reviewed and approved by the institutional review board of the National Health Insurance Service Ilsan Hospital (NHIMC-2019-06-015). The study adhered to the tenets of the Declaration of Helsinki, and the need for written informed consent was waived because of the retrospective study design.

Primary congenital glaucoma registration in South Korea and its definition

All Korean residents are obligated to enroll in the KNHIS, and nearly all of the data in the health insurance system are centralized to a large database. The database includes a record of all medical facilities such as hospitals, private clinics, and public centers in South Korea. Claims include diagnostic codes, personal information, prescription drugs, procedures, information about hospitals, direct medical costs for inpatient and outpatient care, and data on dental services. All charges for KNHIS will be charged through the Korean Electronic Data Interchange code provided by all health care providers. No patient healthcare records are duplicated because all Korean residents receive a unique identification number at birth. Furthermore, the KNHIS uses the Korean Classification of Diseases, which is a system similar to the International Classification of Diseases. The diagnostic code for congenital glaucoma according to the Korean Classification of Disease is Q15.0 (congenital glaucoma), and Q15.0 must be diagnosed within 3 years of birth to be considered primary congenital glaucoma and not juvenile glaucoma. Patients who filed claims for Q15.0 with the KNHIS from January 2001 to December 2015 were included in this study. Primary congenital glaucoma was defined as the presence of buphthalmos, Haab striae, photophobia, loss of corneal transparency, and elevated intraocular pressure with or without optic disc cupping. There was no requirement for anterior segment anomaly.

Statistical analysis

The total, annual, and sex incidence rates were calculated based on the annual number of births presented by the Korean Statistical Information Service (KOSIS, http://kosis.kr). The incidence per person-years was calculated assuming a 1-year follow-up period. To investigate mortality, data for death after primary congenital glaucoma diagnosis were collected, and the follow-up period was from birth year to December 2016. Comorbidity was also examined up to the age of 3 years. The incidence per 100,000 person-years was estimated using the Poisson distribution and presented as a 95% confidence interval. The sex ratio was calculated as the number of female patients divided by the number of male patients per 100,000 people. A sex ratio less than 1 would indicate more cases in male patients than in female patients. All analyses were conducted using Stata/MP ver.14.0 (Stata Corp., College Station, TX, USA).

Results

The total number of primary congenital glaucoma cases that occurred from 2001 to 2015 was 776, comprising 437

Table 1. Incidence of glaucoma per 100,000 person-years among the general Korean population from 2001 to 2015

Year	Total		Male		Female	
	No. of patients	Incidence (95% CI)	No. of patients	Incidence (95% CI)	No. of patients	Incidence (95% CI)
2001	52	9.4 (7.0–12.3)	30	10.4 (7.0–14.8)	22	8.3 (5.2–12.5)
2002	59	12.0 (9.1–15.5)	39	15.1 (10.8–20.7)	20	8.5 (5.2–13.2)
2003	59	12.0 (9.2–15.5)	34	13.3 (9.2–18.6)	25	10.6 (6.9–15.7)
2004	51	10.8 (8.0–14.2)	34	13.8 (9.6–19.3)	17	7.5 (4.4–12.0)
2005	62	14.3 (10.9–18.3)	40	17.7 (12.7–24.1)	22	10.5 (6.6–15.9)
2006	43	9.6 (6.9–12.9)	19	8.2 (4.9–12.8)	24	11.1 (7.1–16.5)
2007	60	12.2 (9.3–15.7)	28	11.0 (7.3–15.9)	32	13.4 (9.2–18.9)
2008	47	10.1 (7.4–13.4)	24	10.0 (6.4–14.9)	23	10.2 (6.5–15.3)
2009	56	12.6 (9.5–16.3)	30	13.1 (8.8–18.7)	26	12.1 (7.9–17.7)
2010	61	13.0 (9.9–16.7)	26	10.7 (7.0–15.7)	35	15.4 (10.7–21.4)
2011	73	15.5 (12.1–19.5)	41	16.9 (12.2–23.0)	32	14.0 (9.6–19.7)
2012	47	9.7 (7.1–12.9)	27	10.8 (7.1–15.8)	20	8.5 (5.2–13.1)
2013	41	9.4 (6.7–12.7)	26	11.6 (7.6–17.0)	15	7.1 (3.9–11.6)
2014	41	9.4 (6.8–12.8)	27	12.1 (8.0–17.6)	14	6.6 (3.6–11.1)
2015	24	5.5 (3.5–8.1)	12	5.3 (2.8–9.3)	12	5.6 (2.9–9.8)
Total	776	11.0 (10.3–11.8)	437	12.0 (10.9–13.2)	339	10.0 (8.9–11.1)

CI = confidence interval.

Table 2. Differences in annual incidence of congenital glaucoma by sex

Year	Male : female ratio	*p*-value (chi-square test)
2001	0.80	0.135
2002	0.56	0.015
2003	0.80	0.099
2004	0.54	0.052
2005	0.59	0.013
2006	1.36	0.094
2007	1.21	0.108
2008	1.02	0.112
2009	0.92	0.127
2010	1.44	0.138
2011	0.82	0.041
2012	0.78	0.080
2013	0.61	0.093
2014	0.55	0.043
2015	1.05	0.159
Total	0.83	0.002

males (56.31%) and 339 females (43.69%) (Table 1). During the study period, the incidence rate was 11.0 per 100,000 births (12.0 for males and 10.0 for females). Annual incidence rates did not fluctuate significantly, but a declining trend has been observed since 2011. With regard to sex-specific patterns, the incidence of male patients varied significantly by year. In comparison, the number of female patients fluctuated only slightly, peaking in 2010. It took an average of 13.81 months to be diagnosed with primary glaucoma after birth.

Intergroup tests were conducted to determine if primary glaucoma was more common in boys (Table 2). Upon chi-square test, with a significance level set at 0.05, the overall incidence was 1.2 times higher in boys.

If we assume that primary congenital glaucoma first occurred around the time of diagnosis, 82% of primary congenital glaucoma cases occurred before the age of 1, similar to the results of previous studies (Table 3). In total, 518 (68.78%) patients were diagnosed at age 0, 112 (13.66%) at 1 year, 70 (8.39%) at 2 years, and 76 (9.17%) at 3 years.

Of the 776 patients diagnosed with primary congenital glaucoma in the study population, 27 died (Table 4). The

Table 3. Incidence of congenital glaucoma by age

Year	Age at the time of diagnosis (yr)			
	0	1	2	3
2001	24 (46.15)	15 (28.85)	8 (15.38)	5 (9.62)
2002	41 (69.49)	10 (16.95)	0 (0)	8 (13.56)
2003	42 (71.19)	7 (11.86)	8 (13.56)	2 (3.39)
2004	40 (78.43)	7 (13.73)	2 (3.92)	2 (3.92)
2005	41 (66.13)	5 (8.06)	9 (14.52)	7 (11.29)
2006	30 (69.77)	4 (9.30)	5 (11.63)	4 (9.30)
2007	33 (55.00)	6 (10.00)	12 (20.00)	9 (15.00)
2008	25 (53.19)	7 (14.89)	4 (8.51)	11 (23.40)
2009	38 (67.86)	3 (5.36)	4 (7.14)	11 (19.64)
2010	32 (52.46)	16 (26.23)	8 (13.11)	5 (8.20)
2011	45 (61.64)	16 (21.92)	5 (6.85)	7 (9.59)
2012	35 (74.47)	4 (8.51)	3 (6.38)	5 (10.64)
2013	32 (78.05)	7 (17.07)	2 (4.88)	0 (0)
2014	36 (87.80)	5 (12.20)	0 (0)	0 (0)
2015	24 (100)	0 (0)	0 (0)	0 (0)
Total	518 (68.78)	112 (13.66)	70 (8.39)	76 (9.17)

Values are presented as number of patients (%).

mean period from diagnosis of primary congenital glaucoma to death was 21.59 ± 29.31 months. In total, 70.4% (n = 19) of these patients died within 3 years of birth, while 29.6% (n = 8) died thereafter. As cause of death data are only available through the KOSIS, cause of death was not analyzed in this study. However, because the time of death was linked to this study data, the annual number of deaths could be identified. We compared the mortality of all infants and children under the age of 4 in KOSIS with the mortality from primary congenital glaucoma. In primary congenital glaucoma patients, there were not many deaths per year, and in some years there were zero deaths. However, the overall mortality per 100,000 people was about 10 times higher than the rate of death for all infants and children under the age of 4.

Among 776 patients with primary congenital glaucoma, 100 had a disability (Table 5). Types of disability included visual impairment, physical disability, brain lesion, hearing impairment, mental retardation, autism, respiratory failure, and facial impairment. Among them, the most common (54%, n = 54) disability was visual impairment, followed by brain lesion and mental retardation.

Table 4. Comparison of mortality rates per 100,000 people between congenital glaucoma patients and the general infant and child population

Year	Congenital glaucoma		General infants and children			
	0–3		0		1–4	
	No. of patients	Mortality	No. of patients	Mortality	No. of patients	Mortality
2001	2	3,846.2	3,006	527.0	1,040	40.1
2002	3	5,084.7	2,542	506.9	1,078	42.9
2003	1	1,694.9	5,214	535.2	814	34.2
2004	3	5,882.4	2,228	484.1	728	32.4
2005	6	9,677.4	1820	420.8	601	28.6
2006	0	0	1,707	407.1	547	28.0
2007	3	5,000.0	1,703	380.6	502	26.9
2008	0	0	1,580	345.5	455	24.7
2009	0	0	1,415	325.7	405	22.0
2010	3	4,918.0	1,508	345.5	386	20.9
2011	0	0	1,435	318.9	389	20.9
2012	0	0	1,405	306.8	377	20.2
2013	3	7,317.1	1,305	294.6	342	18.3
2014	1	2,439.0	1,305	310.2	289	15.4
2015	2	8,333.3	1,190	281.9	287	15.4
Total	27	3,479.4	29,363	400.7	8,240	27.0

Table 5. Types of disability associated with congenital glaucoma

Type	No. of patients
Visual impairment	54
Brain lesions	27
Mental retardation	11
Autism	3
Hearing impairment	2
Physical disability	1
Respiratory failure	1
Facial impairment	1
Total	100

Discussion

Using the KNHIS database, this nationwide, population-based study reported overall, age-, and sex-specific incidence rates of primary congenital glaucoma over a 15-year period. In this study, the Korean incidence of primary congenital glaucoma was 11.0 per 100,000 births. Although some patients may be diagnosed after the age of 3 years, and there are limitations to estimating incidence by diagnostic code, this study is useful in reporting for the first time that about 52 Koreans per year are diagnosed with primary congenital glaucoma.

Based on previous studies, the prevalence of primary congenital glaucoma is between 1 in 10,000 and 1 in 68,254 [7-10]. A population-based study in Spain on congenital eye malformations diagnosed within 3 days following birth, which reported 1,124,654 births from 1980 to 1995, found primary congenital glaucoma in 32 cases, an incidence of 2.85 per 100,000 births [7]. A common definition of primary congenital glaucoma is glaucoma in which intraocular pressure increases within 1 year of birth. Therefore, primary congenital glaucoma in the Spain study, which was diagnosed within 3 days after birth, can be assumed to have a low incidence. The current study might be more accurate because we observed patients for 3 years after birth.

In 2004, there was a report on primary infantile glaucoma among Australians [5]. Data collected from 1980 to 2000 at the Royal Children's Hospital in Melbourne among south-eastern Australians included a total of 51 cases of primary infantile glaucoma, with an estimated incidence based on births in the region of 1 per 30,000 births. The mean age at presentation was 135 ± 84 days, and surgical treatment was performed in nearly 70% of patients; visual outcomes at final review were generally good. In cases diagnosed within 3 months after birth, the patients reported poor visual acuity. This Australian study revealed that boys were twice as likely to be affected as girls. The current study also found that boys represented about 20% more cases than girls, with a similarly high incidence to the Australian study, but a relatively different proportion.

Thus far, no mortalities have been reported from primary congenital glaucoma. According to one meta-analysis, there was no link between primary open-angle glaucoma and risk of all-cause mortality [11]. In this study, mortality was assessed after diagnosis of primary congenital glaucoma, and 27 of 776 patients (3.4%) died. According to the KOSIS, in the national population aged 0 to 4 years, there are 300 to 500 deaths per 100,000 people aged zero years and 15 to 40 deaths between 1 and 4 years. Overall, the trend is decreasing. However, patients diagnosed with primary congenital glaucoma involved a cohort under 3 years of age, which may differ in age from KOSIS data, but on average, 3,500 deaths per 100,000 children were analyzed. These results suggest that primary congenital glaucoma is associated with a 10-fold higher mortality rate than the normal population.

As expected, visual impairment accounts for the largest number of disabilities in patients with primary congenital glaucoma [12,13]. Many studies have reported visual prognosis, with 10% losing sight and about 50% having low vision [14-19]. When diagnosed, a younger age conveys a worse visual prognosis [4]. In the present study, brain lesions were the second highest after visual impairment. It can be assumed that these two disorders may result from the same vascular/neurological diseases, thereby causing many brain lesion disorders in primary congenital glaucoma. According to one population-based study in the United States, congenital heart defects were most common among primary congenital glaucoma patients with multiple defects, followed by central nervous system defects [20]. In a study from Spain, limb anomaly was the most common [7].

This study has several limitations. First, we identified patients with primary congenital glaucoma and other comorbidities based on healthcare claims and Korean Classi-

fication of Disease codes, so this may be relatively inaccurate compared to data obtained directly from medical charts. Second, there are inherent limitations of this research design, as clinical data such as vision, intraocular pressure, and degree of glaucoma progression were not available. Third, the results cannot be generalized to other races/ethnic groups, because this study is based on a population residing in South Korea. Nevertheless, the advantages of this study include the use of national databases, a large sample size, and the potential effects on public health.

In conclusion, the present study reported the incidence rate and characteristics of primary congenital glaucoma among the general Korean population. These findings will help advance our understanding of disease onset and allow healthcare systems to plan for primary congenital glaucoma.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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