communications medicine

A Nature Portfolio journal

Article

https://doi.org/10.1038/s43856-025-01027-x

Lifetime risk, sex and age differences in annual incidence of ocular motor cranial nerve palsy in Japan for 2019

Manabu Miyata[1] ✉, Ai Kido[1], Masahiro Miyake[1], Hiroshi Tamura[1,2], Takuro Kamei[1], Saori Wada[1], Hiroaki Ueshima[2], Shinya Nakao[1], Akinari Yamamoto[1], Kenji Suda[1], Eri Nakano[1], Miho Tagawa[1], Yuki Mori[1] & Akitaka Tsujikawa[1]

Abstract

Background We aimed to demonstrate the incidence and subtype proportions of ocular motor cranial nerve palsy (OMCNP) by age group and sex, and to estimate the associated lifetime risks in the Japanese population.

Methods This nationwide, population-based, cross-sectional cohort study utilized data from the National Database of Health Insurance Claims and Specific Health Checkups of Japan, provided by the Ministry of Health, Labour and Welfare, covering almost all (≥95%) claims. We identified newly diagnosed OMCNP cases (oculomotor, trochlear, or abducens palsy) between January 1 and December 31, 2019, separated by sex and age category (5-year steps). We calculated the incidence rate as the proportion relative to the Japanese population, and calculated the lifetime risk. Furthermore, we calculated the age-standardized incidence rate and lifetime risk according to the world population distribution.

Results The crude incidence rate of OMCNP is 17.36 (oculomotor palsy, 6.62 [38.1%]; trochlear palsy, 2.61 [15.0%]; abducens palsy, 8.14 [46.9%]) per 100,000 person-years. The incidence rate increases with age and is higher in men than in women (19.91 vs. 14.96). The lifetime risks of oculomotor, trochlear, and abducens palsies are 0.50%, 0.19%, and 0.61%, respectively. The age-standardized incidence rates of oculomotor, trochlear, and abducens palsies are 3.25 (lifetime risk, 0.35%), 1.28 (lifetime risk, 0.13%), and 4.60 (lifetime risk, 0.45%) per 100,000 person-years, respectively.

Conclusions This nationwide study of >100 million people reveals that OMCNP incidence increases with age and is higher in men. Approximately one in 100 individuals is affected in their lifetime. Our comprehensive analysis of OMCNP demographics provides important information for addressing healthcare, particularly for older people, from social and public health perspectives.

Plain language summary

Ocular motor cranial nerve palsy is a condition that affects the oculomotor, trochlear, or abducens nerves of the eyes and reduces control of the eye muscles leading to muscle paralysis with subsequent binocular vision disorders. However, no previous study has captured a comprehensive demographic profile. This nationwide population-based cohort study in Japan reveals the annual incidence rates of oculomotor, trochlear, and abducens palsies as 6.62, 2.61, and 8.14 per 100,000 person-years, and the proportions of these conditions as 38.1%, 15.0%, and 46.9%, respectively. The incidence rate increases with age and is higher in men than in women (19.91 vs. 14.96). The lifetime risks of oculomotor, trochlear, and abducens palsies are 0.50%, 0.19%, and 0.61%, respectively. Our comprehensive analysis provides important information for addressing healthcare, particularly for older people, from social and public health perspectives.

Ocular motor cranial nerve palsy (OMCNP), including oculomotor (III), trochlear (IV), and abducens (VI) palsies, induces paralytic strabismus with subsequent binocular vision disorders, which can lead to unsafe driving[1], a musculoskeletal injuries, fractures, or falls[2]. The occurrence of OMCNP is also a risk factor for subsequent stroke (hazard ratio, 4.65)[3]. Therefore, OMCNP may pose a high risk for future physical disability and is thus a condition of social relevance.

The causes of OMCNP are varied and include vascular disorders, aneurysms, head trauma, neoplasms, and congenital disorders[4]. The proportions of these etiologies and clinical features differ between younger and older patients[5]. Furthermore, a previous large cohort study (n = 9682) showed sex differences in excyclo-deviation, partially caused by trochlear palsy, in those aged ≥60 years[6]. Another previous study showed that the mean age of patients with OMCNP was 38.2 ± 19.5 years; however, it

[1]Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Kyoto City, Kyoto Prefecture, Japan. [2]Center for Innovative Research and Education in Data Science, Institute for Liberal Arts and Sciences, Kyoto University, Kyoto City, Kyoto Prefecture, Japan.
✉e-mail: miyatam@kuhp.kyoto-u.ac.jp

included limited cases (n = 345)[7]. Moreover, lifetime risk, i.e., the probability that a person will experience a specific event during their lifetime, has not been reported for OMCNP and can be calculated only by using data across all ages. Therefore, we consider that from a social and public health perspective, capturing a comprehensive demographic profile stratified by age group and by sex is important.

The National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) contains data on almost all (≥95%) health insurance claims in Japan[8], provided by the Japanese Ministry of Health, Labour and Welfare (MHLW), and affords comprehensive overview of real-world clinical practice in this country[9]. We can access the data after the approval of MHLW and have revealed the incidence of strabismus.

In the present study, we determined the incidence rate and lifetime risk of OMCNP by age group and for the sexes separately in the Japanese population using data from the NDB. Furthermore, we calculated the age-standardized incidence rate and lifetime risk, adjusted to the 2000–2025 standard world population distribution as provided by the World Health Organization (WHO).

This nationwide population-based cohort study captures a comprehensive demographic profile of ocular motor cranial nerve palsy, including oculomotor, trochlear, and abducens palsies, which induce paralytic strabismus with subsequent binocular vision disorders. The annual incidence rates of oculomotor, trochlear, and abducens palsies are 6.62, 2.61, and 8.14 per 100,000 person-years. The incidence rate is observed to increase with age and to be higher in men than in women (19.91 vs. 14.96). The lifetime risks of oculomotor, trochlear, and abducens palsies are 0.50%, 0.19%, and 0.61%, respectively. Our results provide important information for addressing healthcare, particularly for older people, from social and public health perspectives.

Methods

The ethics committee of Kyoto University Graduate School of Medicine approved this nationwide, population-based, cross-sectional cohort study (approval no., R2035). All the study protocols adhered to the tenets of the Declaration of Helsinki. Informed consent was waived because this study used anonymous data. We applied to the MHLW to access the NDB, which was approved. This study was conducted during the approved period between August 23, 2021, and February 22, 2022.

Identification of ocular motor cranial nerve palsy cases in the database

We performed this study in the same manner as reported previously[9]. Briefly, we analyzed anonymized data stored in the NDB at the NDB Onsite Research Center Kyoto with the approval of the MHLW. We defined a diagnosis of OMCNP palsy as cases with claim codes related to oculomotor, trochlear, and abducens palsy (details are described in Supplementary Table 1). In Japan, these diagnoses are made by medical doctors. To prevent case duplication, we used a previously reported identification method, in which a newly created ID0 was used to identify the same individual[10].

Annual incidence rate

We counted the number of cases of OMCNP in the NDB who were newly diagnosed between January 1, 2019, and December 31, 2019, separately for each sex and age category (in 5-year steps). We did not include the suspected disease codes. We selected 2019 as the most appropriate year for our investigation because 2019 is the most recent year that we could investigate in the period between 2009 and 2020, except for 2020, when patients hesitated to visit hospitals during the height of the COVID-19 pandemic. Furthermore, the official population statistics in Japan are available to the public on the official website of e-Stat (https://www.e-stat.go.jp/en), which provides the total population on October 1 every year, as estimated using the national population census conducted by the Ministry of Internal Affairs and Communications, separated by sex and age category (in 5-year steps). Thus, the crude annual incidence rate (per 100,000 person-years) of OMCNP in 2019 was calculated as the proportion of the newly diagnosed OMCNP counts relative to the total Japanese population as of October 1, 2019. The proportion of each subtype of OMCNP relative to OMCNP overall was also calculated.

Age-standardized incidence rate

The WHO provides data on the standard world population distribution[11]. Based on Japanese crude incidence rates, we calculated age-standardized incidence rates according to the world population distribution, based on the average world population between 2000 and 2025, as previously reported[12].

Lifetime risk

The lifetime risk, i.e., the integrated incidence risk over a person's lifetime, for each type of nerve palsy was calculated using R (version 4.4.1; R Core Team, Vienna, Austria) and the life table method, as previously reported[13]. This is the longitudinal risk experienced by a person from birth to death. Using this approach is considered more accurate than calculating cumulative risk, as it incorporates the competing risk of death. The mortality rate for the n-th age interval, μ_n, and the incidence rate of the nerve palsy, λ_n, were calculated using the following equations:

$$\mu_n = \frac{N_{Cn}}{N_{Fn}}$$

$$\lambda_n = \frac{N_{Dn}}{N_{Fn}}$$

In these equations, N_{Fn} is the disease-free population at the start of the n-th interval, and N_{Dn} and N_{Cn} are the number of new deaths and new cases during the n-th interval, respectively. Although the calculation requires the mortality rate for the disease-free population, the overall age-specific mortality rate was used as a proxy, as the prevalence of nerve palsy in each age group is extremely low.

For each age interval, the probabilities of transitioning between health states—specifically, from "disease-free" to "disease-affected" and "disease-free" to "death"—were calculated as described below. These probabilities represent the proportion of individuals who change states during a given age interval, specifically indicating the likelihood of developing the disease or of dying without developing the disease.

Disease-free to disease-affected:

$$p_{F\to A,n} = \frac{\lambda_n}{\lambda_n + \mu_n} \times \left(1 - e^{-(\lambda_n+\mu_n)L_n}\right)$$

Disease-free to death:

$$p_{F\to D,n} = \frac{\mu_n}{\lambda_n + \mu_n} \times \left(1 - e^{-(\lambda_n+\mu_n)L_n}\right)$$

In these equations, L_n represents the duration of the n-th age interval in years.

Taking the initial number of individuals at age 0 as the baseline, let $P_{F,n}$ denote the proportion of individuals remaining disease-free by the end of the n-th age interval, and let $P_{A,n}$ denote the proportion of new incidences within the n-th age interval. The following relationships are then derived:

$$P_{F,n+1} = P_{F,n} \times \left(1 - p_{F\to A,n} - p_{F\to D,n}\right)$$

$$P_{A,n+1} = P_{F,n} \times p_{F\to A,n}$$

with the initial conditions:

$$P_{F,0} = 1$$

$$P_{A,0} = 0$$

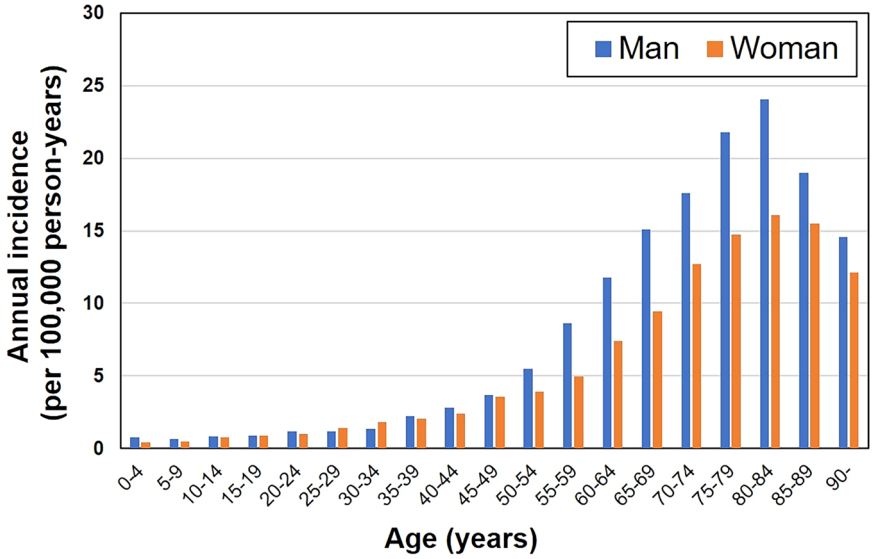

Fig. 1 | Annual incidence rate of oculomotor palsy in each age group. The incidence rate (per 100,000 person-years) increased with age. A marked sex difference (men > women) was observed for those aged over 50 years.

Finally, the lifetime risk is then given by the following equation:

$$\sum P_{A,n}$$

Furthermore, we similarly calculated age-standardized lifetime risk according to the world standard mortality rate provided on the WHO website (https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates).

Statistics and reproducibility

The incidence rates are presented with 95% confidence intervals (CIs) based on a Poisson distribution.

Results

The crude annual incidence rate of OMCNP overall was 17.36 per 100,000 person-years (21,981/126,555,000; 95% CI, 17.14–17.60), including 6.62 per 100,000 person-years (n = 8,378; 95% CI, 6.48–6.76) for oculomotor (III) palsy (Fig. 1, Supplementary Table 2), 2.61 per 100,000 person-years (n = 3,298; 95% CI, 2.52–2.69) for trochlear (IV) palsy (Fig. 2, Supplementary Table 3), and 8.14 (n = 10,305; 95% CI, 7.99–8.30) for abducens (VI) palsy (Fig. 3, Supplementary Table 4). Thus, the proportions of the incidence rate of OMCNP overall accounted for by oculomotor, trochlear, and abducens palsies were 38.1%, 15.0%, and 46.9%, respectively. The incidence rate increased as age increased until approximately 80 years.

When comparing the sexes, we found that the incidence rate of OMCNP overall was higher in men than in women (19.91 [12,262/61,588,000; 95% CI, 19.56–20.26] vs. 14.96 [9,719/64,967,000; 95% CI, 14.66–15.26] per 100,000 person-years), and this difference was particularly marked over middle age (Fig. 4). More specifically, the proportion of the incidence in men relative to that in women was over 1.2 times for those aged over 45 years for oculomotor palsy, over 1.6 times for those aged over 45 years for trochlear palsy, and over 1.2 times for those aged over 40 years for abducens palsy. In other words, no marked sex difference was observed among younger people.

The age-standardized incidence rates of oculomotor, trochlear, and abducens palsies relative to the world population provided by the WHO were 3.25, 1.28, and 4.60 per 100,000 person-years, respectively. Thus, the incidence rate of OMCNP overall was 9.14 per 100,000 person-years. These standardized incidence rates were lower than the corresponding crude Japanese rates.

The crude lifetime risks of oculomotor, trochlear, and abducens palsies were 0.50% (men, 0.53%; women, 0.46%), 0.19% (men, 0.24%; women, 0.14%), and 0.61% (men, 0.66%; women, 0.56%), respectively. Thus, the lifetime risk of OMCNP overall was 1.30%. The age-standardized lifetime risks of oculomotor, trochlear, and abducens palsies were 0.35% (men, 0.37%; women, 0.32%), 0.13% (men, 0.17%; women, 0.10%), and 0.45% (men, 0.48%; women, 0.41%), respectively. Thus, the age-standardized lifetime risk of OMCNP overall was 0.93%.

Discussion

No previous nationwide population-based cohort study on OMCNP has been reported to date. Our study revealed the annual incidence rate of OMCNP, including oculomotor, trochlear, and abducens palsies, for individuals of all ages, as well as separated into 5-year-step age groups, in accordance with the national population census of Japan, using the NDB which was the largest population-based cohort in the world. In our investigation of overall cohort, we found that the incidence rate increased with advancing age and we noted a marked sex difference in the incidence rate (men>women) over middle age. Furthermore, we were able to calculate the lifetime risk, which is a strong point of this study, and revealed that more than one in a hundred people experience OMCNP in their lifetime.

Among the different types of OMCNP, abducens palsy had the highest incidence rate (46.9%), followed by oculomotor palsy (38.1%), and trochlear palsy (15.0%). These rates were similar to those in a previous large-hospital-based study in Japan: 52.9% (117/221), 28.5% (63/221), and 18.6% (41/221), respectively[4]. The chi-square goodness-of-fit test based on the ratio of our results as an almost complete enumeration showed no significant difference between our values and those of the previous Japanese study ($P = 0.10$). However, a prospective multicenter study in the USA (with participants aged ≥50 years) reported rates of 56.9% (62/109), 20.2% (22/109), and 22.9% (25/109), respectively[14], which was significantly different from ours ($P = 0.01$). This might be attributed to racial differences between the study cohorts.

As a premise, the universal health insurance system covers almost all people in Japan; therefore, refraining from visiting hospitals is not likely to have impacted sex differences. The sex difference in the incidence rates (men>women) over middle age in the present study could be attributed to the sex differences in vascular disorders, because a vascular disorder is the most frequent cause of OMCNP in adults aged ≥50 years[4]. In fact, the incidence rate and prevalence of stroke were 33% and 41% higher in men than in women, respectively[15]. Furthermore, the occurrence of OMCNP is a significant risk factor for subsequent stroke[3]. Physicians should understand that the occurrence of OMCNP is higher in older men and should educate patients affected with OMCNP regarding the high risk of future stroke.

The lifetime risk of OMCNP was relatively high, at more than 1%, and most of the patients were older people, aged more than 50 years. Older

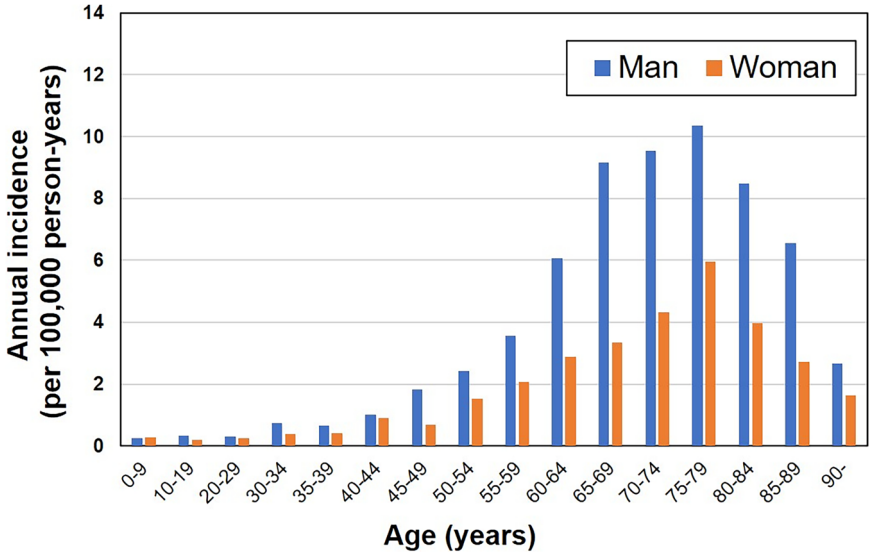

Fig. 2 | Annual incidence rate of trochlear palsy in each age group. The incidence rate (per 100,000 person-years) increased with age. A marked sex difference (men > women) was observed for those aged over 45 years.

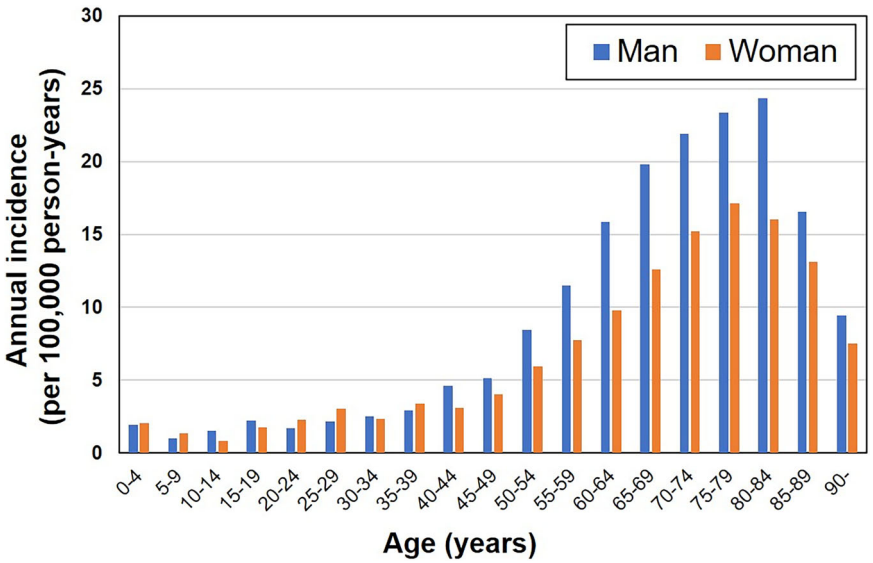

Fig. 3 | Annual incidence rate of abducens palsy in each age group. The incidence rate (per 100,000 person-years) increased with age. A marked sex difference (men > women) was observed for those aged over 40 years.

people are more prone to falls. Falls have adverse consequences for individuals' quality of life and for their families[16], and also pose a substantial financial burden on healthcare systems. A previous study (n = 2,196,881) reported that individuals with disorders of binocular vision, including OMCNP, had significantly higher odds of sustaining musculoskeletal injuries, fractures, or falls (adjusted odds ratio, 1.27; $P < 0.001$)[2]. To prevent such injuries, understanding the relatively high risk of OMCNP and its role in increasing these injuries may be an important step from social and public health perspectives.

In the present study, the incidence of OMCNP increased with age and was rare in young people, particularly in those aged <40 years. However, this finding does not suggest a reduced disease severity in these younger patients; even in these patients, medical examinations, including brain magnetic resonance imaging, are required. The proportions of etiologies of OMCNP differ between younger and older patients. For example, brain neoplasm is a life-threatening disease that was reported to be relatively more common in younger (<49 years) than in older (≥50 years) patients with oculomotor palsy (13% vs. 5%) and trochlear palsy (6% vs. 0%)[4]. Conversely, brain aneurysm, another life-threatening disease, is more common in older than in younger patients with oculomotor palsy (26% vs. 0%)[4]. In our study, we could not obtain information on the cause of OMCNP from the NDB because the diagnosis of OMCNP was not linked to the cause of the condition; therefore, we could not discuss cause and severity. Further research is required from this perspective.

Using the crude Japanese values, we calculated the age-standardized incidence rate and lifetime risk of OMCNP according to the world population distribution provided by the WHO. All of the age-standardized values were lower than the crude Japanese values. We consider that this is due to the notable aging of the Japanese population, in which the rate of older people is higher than in the world population. The information regarding standardized values may be more useful for clinicians in other countries.

This study had some limitations. First, OMCNP data were based on claims codes, as diagnosed by various medical doctors in various regions throughout Japan. No one has assessed the accuracy of the research based on NDB, which would vary for different diseases. Therefore, the validity remains unclear. However, OMCNP is specifically diagnosed based on characteristic findings; therefore, misdiagnosis would be relatively rare. When a patient experiences sudden diplopia due to OMCNP onset, he/she does not hesitate to visit a clinic in Japan because of the universal health insurance system. Miscodes are highly unlikely because clinicians described

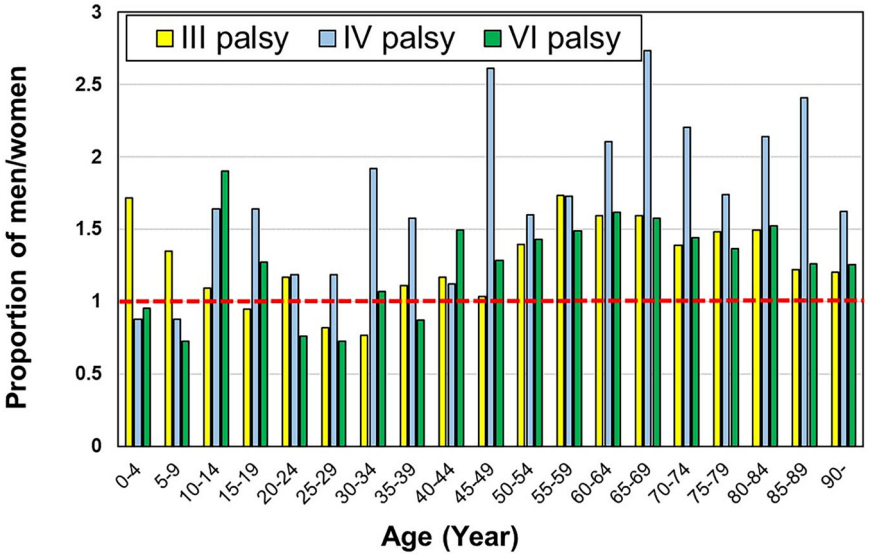

Fig. 4 | Proportion of the incidence of oculomotor cranial nerve palsy in men relative to that in women. The proportion of the incidence in men relative to that in women was over 1.2 times for those aged over 45 years for oculomotor palsy, over 1.6 times for those aged over 45 years for trochlear palsy, and over 1.2 times for those aged over 40 years for abducens palsy. Yellow, blue, and green bars represent oculomotor (III), trochlear (IV), and abducens (VI) palsies, respectively. The red broken line indicates that the proportion of men and that of women are the same.

the diagnosis using the disease name rather than codes. Since physicians sometimes make diagnoses of suspected diseases to claim the costs of examination in Japan, we did not include the suspected disease codes. Second, superior oblique palsy was not included in this study because it involved various conditions not related to the trochlear nerve, such as rectus muscle pulley changes (masquerading as superior oblique palsy) and tendon anomalies[17,18]. Superior oblique palsy also implies congenital etiology; therefore, we considered that it did not match the concept related to OMCNP in this study. However, a certain proportion of superior oblique palsy cases could involve trochlear palsy; therefore, our results regarding trochlear palsy might reflect an underestimation. Third, additional research or modification of the methodology cannot be easily performed due to the stringent study criteria. Fourth, the NDB covers most of the medical care for the entire Japanese population (≥95%)[8]; however, it does not include medical care paid for by welfare or related to industrial accidents. This might have led to an underestimation in our results. Fifth, this study was difficult to investigate the etiology of OMCNP as it was based mainly on the insurance claims and not on clinical judgement of the relationship between OMCNP and its cause; thus, we could not assess the potential impact of confounders. If we conduct further research using the NDB to investigate causes of OMCNP, we will identify other possible causal diseases, including brain neoplasm and brain aneurysm, within three months before and after the diagnosis of OMCNP. However, we consider that the accuracy of the causal relationship is not high. Sixth, this study utilized data that were retrospective in nature. Seventh, this study investigated the general incidence of OMCNP, although this disease population includes a heterogeneous group of patients, with varied age of onset as well as cases that resolve spontaneously. Seventh, patients with OMCNP may die before the diagnosis and after the onset because OMCNP can sometimes be complicated by a severe condition, such as cerebral infarction, which might lead to underestimation.

In conclusion, this nationwide study of >100 million people revealed that OMCNP incidence was higher in older men. Approximately one in 100 individuals is affected in their lifetime. Age-standardized values were lower than crude values, probably due to the progressive aging society in Japan. Our comprehensive analysis of OMCNP demographics provides important information for addressing healthcare, particularly for older people, from social and public health perspectives.

Data availability

All data generated or analyzed during this study are included in this published article. The source data for Figs. 1–3 are in Supplementary Tables 2–4, respectively. The source data for Fig. 4 is in Supplementary Tables 2–4. We applied to the MHLW to access the NDB, which was approved.

Received: 4 November 2024; Accepted: 13 July 2025;
Published online: 19 July 2025

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Acknowledgements

This study was supported in part by grants-in-aid for scientific research from the Japan Society for the Promotion of Science (Nos. 21K09716 to M. Miyata and 21K09740 to H.T., Tokyo, Japan), the Charitable Trust Fund for Ophthalmic Research in Commemoration of Santen Pharmaceutical's Founder 2021 (Osaka, Japan), and The Kyoto University Foundation (Kyoto, Japan). These organizations had no role in the design or conduct of this research.

Author contributions

M. Miyata: conceptualization, methodology, visualization, interpretation, formal analysis, investigation, writing—original draft, writing—review and editing, and funding acquisition. A.K.: conceptualization, methodology, data curation, interpretation, formal analysis, investigation, writing—review & editing. M. Miyake: conceptualization, methodology, interpretation, investigation, writing—review & editing. H.T.: conceptualization, methodology, interpretation, writing—review & editing. T.K.: data curation, interpretation, investigation, writing—review & editing. S.W.: data curation, interpretation, writing—review & editing. S.N.: interpretation, writing—review & editing. A.Y.: interpretation, writing—review & editing. K.S.: interpretation, writing—review & editing. E.N.: interpretation, writing—review & editing. M.T.: interpretation, writing—review & editing. Y.M.: interpretation, formal analysis, investigation, writing—review & editing. A.T.: conceptualization, interpretation, supervision, writing—review & editing.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s43856-025-01027-x.

Correspondence and requests for materials should be addressed to Manabu Miyata.

Peer review information *Communications Medicine* thanks Catherine Jan and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.