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Incidence of cataract surgeries in people with and without Alzheimer's disease

Kaisa Hokkinen,[1] Kai Kaarniranta,[2] Esa Jämsen,[3] Pasi Lampela,[4,5] Sirpa Hartikainen[1] and Anna-Maija Tolppanen[1]

[1]Kuopio Research Centre of Geriatric Care, School of Pharmacy, University of Eastern Finland, Kuopio, Finland
[2]Department of Ophthalmology, Institute of Clinical Medicine, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland
[3]Faculty of Medicine and Health Technology and Gerontology Research Centre GEREC, Tampere University, and Centre of Geriatrics, Tampere University Hospital, Tampere, Finland
[4]Kuopio Research Centre of Geriatric Care, University of Eastern Finland, Kuopio, Finland
[5]School of Pharmacy, University of Eastern Finland, and Finnish Student Health Service, Kuopio, Finland

ABSTRACT.

Purpose: **To investigate the incidence of cataract surgeries in relation to Alzheimer's disease (AD) diagnosis and to compare it with that in people without AD.**

Methods: **The MEDALZ–study includes community-dwelling Finnish persons who received clinically verified AD diagnoses (n = 70718) during 2005–2011 and a matched comparison cohort without AD (n = 70718). The cataract surgeries were identified from the Care Register for Healthcare (1996–2015) using NOMESCO surgical procedure codes CJE (10,15,20,25,99), CJF (00,10,20,30,40,45,50,55,99) and CJG (00,05,10,15,20,25,99). The incidence rates for surgeries per 100 person-years were calculated from 10 years before to 3 years after the index date (date of AD diagnosis from the Special Reimbursement Register).**

Results: **25 763 cataract procedures were performed on persons with AD and 26 254 on persons without AD during the follow-up. The incidence of surgery increased similarly in both groups before the index date of AD diagnosis, and the rate of surgery was similar in people with and without AD (3.5 and 3.3/100 person-years, respectively). The incidence diminished steeply in the AD group already one year after the index date, whereas the slow increase continued in the non-AD group. After the index date, the rates were 3.7 and 4.7/100 person-years in people with and without AD.**

Conclusion: **The diminishing surgery rate very soon after AD diagnosis is concerning. The stigma of AD diagnosis may lead to fewer referrals to surgery, although these patients are expected to benefit from surgery.**

Key words: Alzheimer's disease – cataract surgery – dementia – ageing and surgery

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Introduction

The prevalence of Alzheimer's disease (AD) has increased globally during the last decades (Feigin et al. 2019). It is well known that suboptimal care of comorbidities can accelerate the course of cognitive decline in AD (Doraiswamy et al. 2002). One of these comorbidities, poor vision, is associated with cognitive decline (Lin et al. 2004; Roger & Langa 2010). The most common cause of poor vision and vision loss is cataract, where the opacity of the crystalline lens of the eye is lost. The only treatment is rather mini-invasive surgery (Crandal 2001; Asbell et al. 2005). Previous studies have shown that persons with cognitive disorders are less likely to undergo cataract surgery than those with normal cognition (Goldacre et al. 2015; Wu et al. 2018; Pershing et al. 2019; Stagg et al. 2019). All these studies included people who had already been diagnosed with cognitive disorder. Therefore, it is not known when this difference emerges, and whether it is evident already during the prodromal period or at the early stages of cognitive disorders.

We performed a nationwide study of community-dwelling residents who received a clinically verified AD diagnosis in Finland in 2005–2011. Our aims were to estimate the incidence of cataract surgery in relation to AD diagnosis among persons with AD and to compare it with that in people without AD.

Materials and methods

Study design and cohort

The MEDALZ cohort includes residents of Finland who received a

clinically verified AD diagnosis during 2005–2011 and were community-dwelling at the time of the diagnosis. The cohort consists of 70,718 persons with AD, with an age range from 35 to 105 and mean age of 80.1 years; 65% of them were women. The study cohort and data sources have been described previously (Tolppanen et al. 2016).

Data in the study were extracted from the Finnish nationwide healthcare registers, including the Prescription Register (1995–2015; purchased prescription drugs in Finnish pharmacies), the Special Reimbursement Register (1972–2015; chronic comorbidities), the Hospital Discharge Register (1972–2015; diagnoses and procedures of hospital admissions) and the Statistics Finland (mortality 2005–2015, and socioeconomic data from 1972 to 2012). All data were de-identified before sending to research team, and participants were not contacted. Therefore, according to Finnish legislation, ethics committee approval or informed consent were not required. The study adhered to the tenets of the Declaration of Helsinki.

Identification of AD and comparison cohorts

Persons with incident AD diagnosis were identified from the Special Reimbursement Register which is maintained by the Social Insurance Institution of Finland (SII). To get the special reimbursement for AD, the patients had to fulfil explicit predefined criteria. Written documentary evidence, including results of diagnostic tests, had to be provided to the SII by the treating physician. The diagnostic criteria of AD were based on NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) and DSM-IV criteria for AD (Diagnostic and Statistical Manual Fourth edition) (McKhann et al. 1984; McKhann et al. 2011). All AD cases had to fulfil the requirements for the reimbursement of AD drugs which are as follows: (i) symptoms consistent with AD; (ii) a decrease in social capacity over a period of at least 3 months; (iii) received a computed tomography/magnetic resonance imaging scan; (iv) had possible alternative diagnoses excluded and (v) received confirmation of the diagnosis by a registered neurologist or geriatrician. Patients with mild to moderate AD were entitled to reimbursed medication. Hence, the MEDALZ cohort contains persons with mild to moderate stage of AD at the time of diagnoses. It was also confirmed whether the patient had other dementing diseases, such as mixed dementia, multi-infarct dementia or Lewy body dementia. These patients were entitled to reimbursed medicines if the symptoms were considered to be mainly caused by AD.

Each person in the AD cohort was matched with one comparison persons without AD by age ($\pm$1 year), sex and region of residence at the date of AD diagnosis (index date). The matched controls were identified from nationwide registers of the SII including all residents with the following criteria: (i) alive and community-dwelling during the last day of the month when case was diagnosed with AD (index date); (ii) no special reimbursement for AD medication, or purchases of acetylcholinesterase inhibitor or memantine (ATC code N06D) before index date and within 12 months after it. The drug purchases were identified from the Prescription Register, also maintained by the SII. The register contains information on all reimbursed prescription purchases for community-dwelling persons, including data on drug, dispensing date, number of packages, strength, package size and dispensed amount in defined daily doses.

Identification of cataract surgeries

The procedures were identified from the Care Register for Healthcare (1996–2015) using The Nordic Medico-Statistical Committee (NOMESCO) surgical procedure codes. The most common cataract procedure is the phacoemulsification with implantation of artificial lens in posterior chamber, corresponding to the NOMESCO code CJE20. The other codes CJE (10,15,25,99), CJF (00,10,20,30,40,45,50,55,99) and CJG (00,05,10,15,20,25,99) are mainly used for complex diseases or complication with this regular cataract surgery (M.-S. Nordic-Committee 2010). In the main analyses, we investigated the incidence of cataract surgery (CJE20). People with one previous CJE20 surgery were included. Those with two CJE20 operations before the follow-up were excluded from analyses. Sensitivity analyses were performed for first cataract surgery (no previous surgeries) and for any cataract-related surgery (any procedure code).

Other characteristics

Data on comorbidities were extracted from the Finnish nationwide healthcare registers which include both public and private healthcare services. These registers included the Special Reimbursement Register and the Hospital Discharge Register. The comorbidities asthma or COPD, rheumatoid arthritis and related connective tissue diseases, diabetes, cardiovascular diseases (including hypertension, coronary artery disease and heart failure) were based on the Special Reimbursement Register and glaucoma, diabetic retinopathy, age-related macular degeneration, blindness or amblyopia and presbyacusis on the Hospital Discharge Register. The Hospital Discharge Register contains information on inpatient days in primary and specialized hospitals. The information of each hospital visit includes dates and diagnoses coded according to International Classification of Diseases, Eighth Revision [ICD-8] until 1986, ICD-9 in 1987-1995 and ICD-10 since 1996. Additionally, socioeconomic position, defined as the highest occupational social class in middle age, was obtained from the censuses maintained by the Statistics Finland. The highest occupational position (managerial/professional, office, farming/forestry, sales/industry/cleaning and unknown) reported were taken for each person.

Statistical analysis

Descriptive statistics were carried out using means, standard deviations (SD) and percentages. The results are presented with 95% confidence intervals (CIs). To compare characteristics between groups, an independent sample t-test for continuous variables with normal distribution, and chi-square test for categorical variables were applied.

The rate of surgery per 100 person-years was calculated for every 6-month period starting from 10 years before and until three years after the index date by using stptime command of

STATA. The confidence intervals were calculated using the quadratic approximation to the Poisson log likelihood for the log-rate parameter. The follow-up ended on surgery, death or at the end of study follow-up (three years after AD diagnosis). In addition, comparison persons were censored on the date of eventual AD diagnosis. All statistical analyses were performed using the software STATA 14 (Stata Corporation, College Station, TX, USA).

Results

Characteristics

Altogether 25 763 cataract procedures were performed on persons with AD and 26 254 on persons without AD during follow-up. Majority of procedures was performed before the index date: 21 016 on persons with AD and 20 031 without AD (Table 1). The mean age in persons with cataract surgery was the same in persons with AD (82.9 years) and without AD (83.0 years). In the cataract surgery groups, there was no difference in the socioeconomic status between persons with and without AD. Only a minority of persons with AD ($n = 830$) and without AD ($n = 756$) who had a cataract surgery before index date had already been operated on (CJE20) before the beginning of the follow-up. Altogether 4747 cataract surgeries were performed on persons with AD and 6223 on persons without AD after the index date.

Other eye diseases (glaucoma, diabetic retinopathy, age-related macular degeneration, blindness or amblyopia) were common in both persons with and without AD (Table 1). They were roughly twice as common in those who had cataract surgery. Presbyacusis and other comorbidities were more prevalent among those who had cataract surgery, regardless of whether they had AD.

There was no clinically important difference in the age at cataract surgery (Table 2). The differences in the prevalence of glaucoma, diabetic retinopathy and age-related macular degeneration among persons who had cataract surgery were not significant between groups.

Incidence of cataract surgery

The incidence of cataract surgery increased from approximately 2 surgeries/100 person-years ten years before index date to 4.5/100 person-years at the time of the index date among both persons with and without AD (Fig. 1).

Table 1. Characteristics of people with and without Alzheimer's disease according to cataract surgery

	Alzheimer's disease N = 70718			No Alzheimer's disease N = 70718		
Cataract surgery before the index date	Yes, N = 21016	No, N = 44955	p-value	Yes, N = 20031	No, N = 44464	p-value
Cataract surgery before follow-up	830 (4.0)	1477 (3.0)	<0.001[a]	756 (3.8)	1307 (2.6)	<0.001[a]
Age at index date mean, 95 % CI	82.9 (82.8-83.0)	78.8 (78.8-78.9)	<0.001[b]	83.0 (82.9-83.0)	78.9 (78.8-79.0)	<0.001[b]
Sex			<0.001[a]			<0.001[a]
-Women	15383 (73.2)	30733 (61.8)		14838 (74.1)	31278 (61.7)	
Highest occupational class before follow-up			<0.001[a]			<0.001[a]
-managerial/ -profession	3807 (18.1)	10885 (21.9)		3760 (18.8)	11409 (22.5)	
-office	1837 (8.7)	4136 (8.3)		1833 (9.2)	4107 (8.1)	
-farming, forestry	3963 (18.9)	9476 (19.1)		3960 (19.8)	9828 (19.4)	
-sales, industrial, cl	9050 (43.1)	21098 (42.5)		8166 (40.8)	19367 (38.2)	
-unknown	2359 (11.2)	4197 (8.3)		2312 (11.5)	5976 (11.8)	
Comorbidities before follow-up:						
Eye diseases						
-Glaucoma	6228 (29.6)	7725 (15.5)	<0.001[a]	6543 (32.7)	8739 (17.4)	<0.001[a]
-Diabetic retinopathy	421 (2.0)	453 (0.9)	<0.001[a]	339 (1.7)	287 (0.6)	<0.001[a]
-Age-related macular degeneration	46 (0.2)	47 (0.1)	<0.001[a]	49 (0.2)	50 (0.1)	<0.001[a]
-Amblyopia/blindness	159 (0.8)	192 (0.4)	<0.001[a]	188 (0.9)	175 (0.4)	<0.001[a]
Other comorbidities						
-Any cardiovascular disease	11696 (55.7)	23475 (47.2)	<0.001[a]	11400 (56.9)	22928 (45.2)	<0.001[a]
-Diabetes	3093 (14.7)	6367 (12.8)	<0.001[a]	2793 (13.9)	5183 (10.2)	<0.001[a]
-Asthma/COPD	2342 (11.1)	3857 (7.8)	<0.001[a]	2199 (11.0)	4015 (7.9)	<0.001[a]
-Rheumatoid arthritis	1200 (5.7)	1985 (4.0)	<0.001[a]	1150 (5.7)	2016 (4.0)	<0.001[a]
-Presbyacusis	1164 (5.5)	1740 (3.5)	<0.001[a]	1123 (5.6)	1472 (2.9)	<0.001[a]

Data are given as N (%) unless otherwise indicated.
[a] Chi-square test.
[b] Two-sample t-test with equal variances.

Table 2. Characteristics and comorbidities of people who have undergone cataract surgery according to AD status

	Alzheimer's disease N = 25763	No Alzheimer's disease N = 26254	p-value for difference between persons with AD vs. persons without AD who have undergone cataract surgery
Age at surgery mean, 95 % CI	78.8 (78.7–78.8)	79.2 (79.2–79.3)	<0.001[b]
Comorbid eye diseases before operation N (%)			
-*Glaucoma*	4672 (18.1)	5385 (20.5)	<0.001[a]
-*Diabetic retinopathy*	344 (1.3)	265 (1.0)	0.001[a]
-*Age-related macular degeneration*	34 (0.1)	40 (0.2)	0.537[a]
-*Amblyopia/blindness*	83 (0.3)	77 (0.3)	0.552[a]
Presbyacusis N (%)	798 (3.1)	830 (3.2)	0.675[a]
Other comorbidities before operation N (%)			
-*Asthma/COPD*	2506 (9.7)	2536 (9.6)	0.794[a]
-*Rheumatoid arthritis*	1290 (5.0)	1344 (5.1)	0.560[a]
-*Diabetes*	3177 (12.3)	2880 (11.0)	<0.001[a]
-*Any cardiovascular disease*	13370(51.9)	13751(52.4)	0.273[a]

[a] Chi-square test.
[b] Two-sample t-test with equal variances.

Before the index date, the rates were 3.5 (95% CI 3.4–3.6) and 3.3 (95% CI 3.2-3.3) surgeries/100 person-years in people with and without AD, respectively. After AD diagnosis, the rates were 3.7 (95% CI 3.6–3.8) and 4.7 (95% CI 4.6–4.8) surgeries/100 person-years. Already one year after the AD diagnosis, the incidence of cataract surgery started to diminish steeply among persons with AD, whereas the incidence of surgery slowly continued to grow among persons without AD (Fig. 1). At that time-point, the incidence rate ratio was 16% lower for people with AD (0.84, 95% CI 0.77–0.92, rate of surgery 4.0, 95% CI 3.7–4.2 for people with AD and 4.7, 95% CI 4.4–5.0 for people without AD) A similar phenomenon is seen in the incidence of the first cataract surgery and any cataract surgery. (Data not shown).

Discussion

We found that the incidence of cataract surgery among persons with AD started to decrease shortly after AD diagnosis and continued on this course until the end of the follow-up period whereas the incidence of cataract surgery continued to grow among persons without AD. There are earlier studies on cataract surgery rates among persons with dementia (Goldacre et al. 2015; Wu et al. 2018; Pershing et al. 2019; Stagg et al. 2019) but to our knowledge, ours is the first to describe the temporal changes in incidence, and to assess incidence before AD diagnosis.

The difference in the rate of surgeries began to emerge after the index date/AD diagnosis. The lower likelihood of cataract surgery among people with dementia has been reported previously (Goldacre et al. 2015; Wu et al. 2018; Pershing et al. 2019; Stagg et al. 2019). An English study showed lower treatment rates for cataract among persons with dementia and a decrease in surgery rate with length of time from diagnosis of dementia (Goldacre et al. 2015). Similar finding was made in a study of US Medicare patients (Pershing et al. 2019). Similarly, in our study the likelihood of surgery declined as the time from AD diagnosis increased. Two other American studies also reported an association between dementia diagnosis and a smaller likelihood of cataract surgery (Wu et al. 2018; Stagg et al. 2019). These studies encompassed persons with many types of dementias and persons with abnormal cognitive test results (Goldacre et al. 2015; Wu et al. 2018; Pershing et al. 2019; Stagg et al. 2019). Our results are not fully comparable to them because we focused on persons with a clinically verified Alzheimer's disease. Further, the relative risk difference in these previous studies was larger than in ours which is most likely explained by the difference in follow-up duration. We limited our follow-up to three years after AD diagnosis because persons with AD had mild to moderate AD at the time of diagnosis. We reasoned that these persons could benefit most from surgery before their cognitive skills deteriorate as AD progresses over time. Considering this, it is difficult to find adequate reasons for the decrease in surgery rates in our study population.

The finding that persons with AD are less likely to have cataract surgery is unlikely explained by comorbidities, as their associations with surgery were similar between people with and without AD. The result is clinically significant because AD causes visual

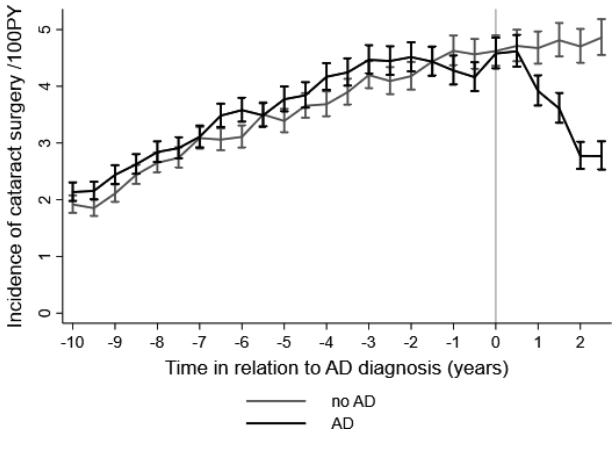

Fig. 1. Incidence of cataract surgery (CJE20) in relation to AD diagnosis.

disturbances among other cognitive problems (Cerquera-Jaramillo et al. 2018). These include decreased contrast sensitivity, visual attention skills and constructional and visuoperceptual disorientation (Kusne et al. 2017; Cerquera-Jaramillo et al. 2018). Poor vision due to cataract might go unnoticed if visual and visuospatial cognitive problems are dominant.

This study showed that other eye diseases were roughly twice as common in the cataract surgery groups than in the no-surgery groups, in both persons with and without AD. One explanation might be that persons with these conditions are often followed up by an ophthalmologist, and cataract is diagnosed during follow-up visits. It is also possible that persons referred for cataract surgery receiving a preoperative ophthalmologic examination are simultaneously diagnosed with other eye diseases. Additionally, the Finnish Current Care Guideline for cataract states that cataract surgery can facilitate the follow-up of glaucoma or diabetic retinopathy as reduced opacity of the lens might hinder this (The Finnish Medical Society Duodecim, 2019). Cataract surgery decreases the intraocular pressure and can be used for treating glaucoma (Falck et al. 2011). Vitreoretinal surgeries inevitably cause cataract and sometimes cataract phacoemulsification is performed proactively on patients undergoing these procedures (Belin & Parke 2020). These aspects might result in cataract operations partly due to eye comorbidities. We also found that other comorbidities such as cardiovascular diseases and diabetes were more common in the cataract surgery group. Maybe these comorbidities increase contacts to health care professionals, which in turn facilitates cataract diagnoses.

The decrease in the incidence of cataract surgeries among persons with newly diagnosed AD is concerning and has clinical implications. In Finland AD is mainly diagnosed by geriatricians in older adults over age 65. Assessment of sensory deficits including visual impairment is an essential part of the diagnostic assessment. Therefore, one would expect more referrals to cataract surgeries at the time of AD diagnosis, particularly because visual impairment is associated with the deterioration of cognitive skills (Lin et al. 2004; Roger & Langa 2010) and cataract surgery might improve cognitive functioning in persons with cognitive disorders (Tamura et al. 2004). Cataract surgery can also increase physical activity (Meuleners et al. 2019) and prevent falls (Brannan et al. 2003; Harwood et al. 2005; Feng et al. 2018), even though there are also conflicting findings that it might increase risk of falls (Meuleners et al. 2012; Meuleners et al. 2014). We should identify persons who would benefit from surgery when their cognitive problems are still relatively mild.

All professionals working with AD patients are probably not familiar with cataract procedures and might overestimate the risks, and therefore, they will not actively refer patients to ophthalmologic consultations. The stigma of AD diagnosis may also lead to fewer referrals to surgery. However, the procedure is mini-invasive (Crandal 2001) and general anaesthesia is rarely used (Jefferis et al. 2014). Therefore, it is unlikely that ophthalmologists would refuse cataract surgery from persons with mild or moderate cognitive problems.

A strength of this study is that it covers all community-dwelling persons with AD in Finland during the follow-up period making the study cohort representative and generalizable to AD population. Another strength is that all used health registers were nationwide and the Care register for healthcare covers surgeries both in public and private hospitals. A weakness of the study is that we have no knowledge of the stage of AD at the time of AD diagnosis or the cataract surgery; however, the MEDALZ cohort itself only contains persons with mild to moderate stage of AD at the time of AD diagnoses.

In conclusion, persons with newly diagnosed AD are less likely to have cataract surgeries than persons without AD. This is concerning because surgical management of cataract might improve cognitive functioning in persons with AD and this treatable visual problem might go unnoticed due to visual disturbances caused by the cognitive disorder itself. Geriatricians and general practitioners hold a key role in determining the risks and benefits of referral to the surgery when it comes to older adults with cognitive problems which should be emphasized in the clinical practice. Professionals working with patients with AD should be encouraged to actively refer patients to ophthalmologic consultations. The stigma of the disease should not lead to fewer referrals to cataract surgery.

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Correspondence:
Kaisa Hokkinen, MD
University of Eastern Finland - Kuopio Campus
Kuopio Research Centre of Geriatric Care
Yliopistonranta 1
70210 Kuopio
Finland
Tel: +3584074949
Email: k.hokkinen@gmail.com

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