The Prevalence of Nystagmus: The Leicestershire Nystagmus Survey

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Purpose. Nystagmus, which can be infantile (congenital) or acquired, affects all ages. The prevalence of nystagmus in the general population is unknown. New genetic research and therapeutic modalities are emerging. Previous estimates have been based on wider ophthalmic epidemiologic studies within specific occupational or age groups. The authors carried out the first epidemiologic study to specifically establish the prevalence of nystagmus in Leicestershire and Rutland in the United Kingdom.

Methods. Three independent data sources identified persons with nystagmus from the hospital and community. The first was a hospital-based questionnaire and clinical survey (n = 238). The visually impaired services (n = 414) and education services (n = 193) in Leicestershire provided the second and third separately obtained community-based sources of information. Capture-recapture statistical analysis was used to estimate prevalence.

Results. The prevalence of nystagmus in the general population was estimated to be 24.0 per 10,000 population (95% confidence interval [CI], ±5.3). The most common forms of nystagmus were neurologic nystagmus (6.8 per 10,000 population; 95% CI, ±4.6), nystagmus associated with low vision such as congenital cataracts (4.2 per 10,000; 95% CI, ±1.2), and nystagmus associated with retinal diseases such as achromatopsia (3.4 per 10,000 population; 95% CI, ±2.1). Within ethnic groups, nystagmus was significantly more common in the white European population than in the Asian (Indian, Pakistani, other Asian backgrounds) population (P = 0.004).

Conclusions. The findings suggest that nystagmus is more common in the general population than previously thought. This may be of significance in resource allocation and health care planning. (*Invest Ophthalmol Vis Sci.* 2009;50:5201–5206) DOI:10.1167/iovs.09-3486

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Nystagmus consists of rhythmic involuntary oscillations of the eyes. It can occur in early childhood (infantile nystagmus) or can be acquired later in life (acquired nystagmus). The main groups of infantile nystagmus are unassociated/pure infantile nystagmus syndrome (INS; which was widely known as idiopathic infantile nystagmus), INS associated with albinism, fusion maldevelopment nystagmus syndrome (FMNS; which has previously been described as latent/manifest latent nystagmus), spasmus nutans syndrome, and nystagmus associated with ocular disease.[1]

Acquired nystagmus occurs mainly in neurologic and vestibular diseases. With the exception of vestibular nystagmus, which is most frequently caused by inner ear semicircular canal dysfunction, nystagmus is likely to result from abnormal development or pathologic malfunction of areas in the brain controlling eye movements and gaze stability or afferent pathway disorders.[2] New pharmacologic[3–12] and surgical[13,14] treatments for nystagmus are emerging. The understanding of pathologic mechanisms in nystagmus is improving. In X-linked unassociated INS, we have recently identified mutations in a novel gene (*FRMD7*).[15] By analogy with other FERM proteins, loss of *FRMD7* may alter neurite growth and branching in neuronal tissue.

The impact of nystagmus on vision can be significant, with visual function in many patients scoring worse than in patients with age-related macular degeneration.[16] However, the prevalence of nystagmus in the general population is unknown. No other studies have had the primary aim of estimating the prevalence of nystagmus in the general population. Previous estimates of nystagmus prevalence have been obtained from a cohort of partially sighted or blind children older than 15 years in Denmark,[17] among 220,802 army recruits (excluded from service because of poor vision) in the Netherlands,[18] in all children attending the first grade of the elementary schools of Malmö, Sweden between 1941 and 1959, with further examination of family members of affected children,[19] and in a representative sample of 15,000 10-year old children in the United Kingdom.[20] Two of these studies looked at the incidence of all varieties of infantile nystagmus within a selected group of persons with poor vision,[17,18] whereas one study examined only children with nystagmus and their affected family members, thus excluding adults with nonfamilial forms of nystagmus.[19] A further study looked at a representative sample of 15,000 children aged 10 years with visual acuities ranging from 20/20 to poorer than 20/200.[20] None of these studies provided data on adults or children with acquired nystagmus.

The aim of our study was to specifically estimate the prevalence of nystagmus, including all nystagmus forms (with the exception of transient vestibular nystagmus), in Leicestershire and Rutland, United Kingdom, with a population of just fewer than 1 million people. We used capture-recapture (CRC) statistics with three different sources of data. Leicestershire and Rutland is a good setting for an epidemiologic study because previous locally conducted ophthalmic research has shown that only a small number of patients obtain their eye care

outside the county (Deane JS, et al. *IOVS* 1998;39:ARVO Abstract 2117).[21]

METHODS

The study received ethical approval from the Leicestershire ethics committee and adhered to the tenets of the Declaration of Helsinki. We performed a countywide survey within Leicestershire and Rutland (population, 925,000[22]; 1.88% of the total population of England). Leicestershire (including Leicester city) and Rutland are situated in the center of the East Midlands of England. The land area of Leicestershire is 2553 km^2. The ethnic minority community of Asian/Indian origin accounts for 29.9% in Leicester city, 3.7% in Leicestershire (excluding Leicester city), and 0.4% in Rutland.[22] This corresponds to 11.5% of the total county's population. For the CRC statistics, data were collected for the three sources through August 14, 2003.

Leicester Nystagmus Survey (LNS)

Countywide (Leicestershire and Rutland) recruitment formed a hospital-based survey whereby all hospital specialists, general practitioners, community optometrists, and teachers for the visually impaired were invited to inform patients with nystagmus about the study and to ask them to participate. All existing databases from the hospital were searched, and patients with nystagmus were invited to participate (GW had a database of all diagnoses of children he has seen since 1995, and IG had a database of all patients she has seen in pediatric and adult neuro-ophthalmology clinics since 1999). In addition, there was media publicity using local newspapers and radio channels and talks to the local optometry association.

All identified patients were invited for a detailed clinical examination, including assessment of vision, refractive error, and funduscopy. Informed consent was obtained from all participants in the community and hospital-based survey. Video and eye movement recordings (n = 198) and electrodiagnostic (n = 62) testing were carried out, where indicated, to aid with clinical diagnosis. Some patients underwent all three investigations. Twenty-eight patients did not attend for clinical assessment, but all consented to a review of their clinical notes and previous investigations to establish a clinical diagnosis. Seven patients who were referred by neurologists but who were not current ophthalmology patients were seen by an ophthalmologist to confirm the diagnosis, according to the protocol requirements. Patients who attended the local hospital services but were living outside the designated boundaries of the county were excluded from the study. In the LNS group, patients were asked to state their ethnicity using the same classification as in the national UK census. We compared the ethnic distribution of patients with nystagmus from Leicester city to the distribution of ethnic groups within the population of Leicester city obtained from the last census.[22] People from white British and other white backgrounds were grouped together as the "white population" group and were compared with the "Asian population" from Indian, Pakistani, Bangladeshi, and a minority from other Asian backgrounds.

The final classifications of the different types of INS were based on a combination of clinical assessment, electrodiagnostics, eye movement recordings, and radiologic tests. Unassociated INS was diagnosed in patients with nystagmus who had normal ocular examination and electrodiagnostic test results. The diagnosis of INS plus albinism was made based on the presence of one or a combination of the following clinical features in addition to nystagmus: iris transillumination, macular hypoplasia, fundus hypopigmentation, and visual evoked potential asymmetry. FMNS was distinguished from unassociated INS by the reversal in direction and the increase in amplitude of nystagmus on occlusion of either eye and the presence of linear or decelerating velocity waveforms in the slow phase in FMNS, in contrast to increasing velocity waveforms in unassociated INS. Spasmus nutans syndrome was diagnosed in patients with the triad of nystagmus, head nodding, and anomalous head positions.

Society for Visually Impaired Individuals (VISTA)

An independent source of persons with nystagmus was obtained from VISTA using blind and partially sighted registration details held by the society of all persons living within the county of Leicestershire and Rutland. Registration with VISTA is voluntary but carries with it benefits, including practical support from social services, concessions, and in some cases financial support. The criterion for registration is based on national standards that take into account visual acuity and field of vision.[23] There were 5885 persons registered as blind or partially sighted within the county up to and including August 14, 2003. Before September 2005, blind and partially sighted registration forms were known as BD8 registration forms and contained information about the patient's ocular diseases. The final clinical diagnosis was obtained from registration forms for 2358 persons. In the remaining 3527 registered persons, 498 had missing registration forms, 424 had recently died before August 14, 2003 (and were excluded), and 2705 had forms that did not contain any clinical information and hospital notes had been destroyed. After this, the hospital records of all patients who had a possible diagnosis associated with nystagmus or for whom the diagnosis was poorly recorded (n = 1873) were examined to confirm the presence or absence of nystagmus. If hospital records were not obtained (n = 202), further information was obtained from correspondence letters sent to general practitioners by the hospital ophthalmologist. Records confirming the diagnosis were found for all patients.

Leicestershire Educational Services (Education)

Data were obtained from the education services for the visually impaired within the county. Teachers provided details of pupils with nystagmus who were under their care (including elective home education children) and whose notes were reviewed to verify the diagnosis of nystagmus and to classify the nystagmus. For all pupils in this group, hospital notes were found. All persons within this data collection group were 18 years or younger on August 14, 2003.

Statistical Analysis

We identified patients with nystagmus who had registered with only one source (e.g., hospital survey), two sources (e.g., hospital survey and VISTA), or all three sources. After identifying the overlaps (patients whose names appeared on more than one database source), we used CRC methods[24] (with GLIM[25] software) to establish the number of nystagmus individuals not recorded by any of these three sources (i.e., "uncaptured" individuals with nystagmus). In the group younger than 18 years, analysis was carried out using three data sources—hospital, visually impaired registration, and education services. For the group older than 18 years, CRC analysis was carried out using two sources of data, the hospital survey and visually impaired registration groups.

CRC was also used to estimate the prevalence of the most common forms of nystagmus (unassociated INS, INS associated with albinism, INS associated with retinal diseases, INS associated with low vision, neurologic) and in groups 18 years of age or younger and older than 18. It was not possible to use CRC in less common forms of nystagmus (INS associated with ocular disease, FMNS, other infantile forms, spasmus nutans, neurologic nystagmus in children, neurologic nystagmus forms other than multiple sclerosis and stroke in adults, unknown etiology) because there was no overlap between sources.

Pearson's χ^2 tests were performed to compare the distribution of nystagmus within ethnic groups within the population of Leicester city (obtained from the last census [2001])[22] based on the LNS database, in which we had data from all questionnaire participants. We did not have data on ethnicity from the VISTA or education databases.

RESULTS

The hospital-based survey (LNS) located 238 of 241 known patients with nystagmus. One patient withdrew after initial consent. Two other participants who attended the survey after

media publicity were excluded from the study because they did not have nystagmus. Figure 1 shows the frequency of the different clinical types of nystagmus in the patients with LNS. There were 111 male and 127 female patients. The most common type of nystagmus identified by the survey was unassociated INS (50 patients).

The records of blind and partially sighted patients registered in Leicestershire identified 414 (242 males, 172 females) with various types of nystagmus. Unlike the hospital patients, most of these patients had nystagmus with associated ocular diseases such as congenital cataracts, optic nerve hypoplasia, and nystagmus associated with retinal diseases, such as achromatopsia and congenital stationary night blindness, all of which cause variable but significant visual impairment (Fig. 1). Other congenital forms of nystagmus include unilateral microphthalmos, bilateral aniridia, and congenital syndromes.

The third source of independent information, the education services, found 193 individuals (111 females, 82 males) with nystagmus (primarily infantile forms) that were almost equally distributed among INS associated with albinism, unassociated INS, INS associated with low vision, and retinal diseases (Fig. 1). Among the children with neurologic nystagmus, most cases were associated with neurologic syndromes such as Down syndrome or septo-optic dysplasia or with congenital neurologic anomalies such as hydrocephalus or microcephalus.

After independent ascertainment of patients with nystagmus from all three sources, the overlapping patients in each source were identified (Figs. 2A, 2B).

CRC analysis was used to estimate that 29 individuals were not identified by the three data sources in the group 18 years of age or younger, giving the total number of individuals 18 years of age or younger with nystagmus as 396 (95% confi-

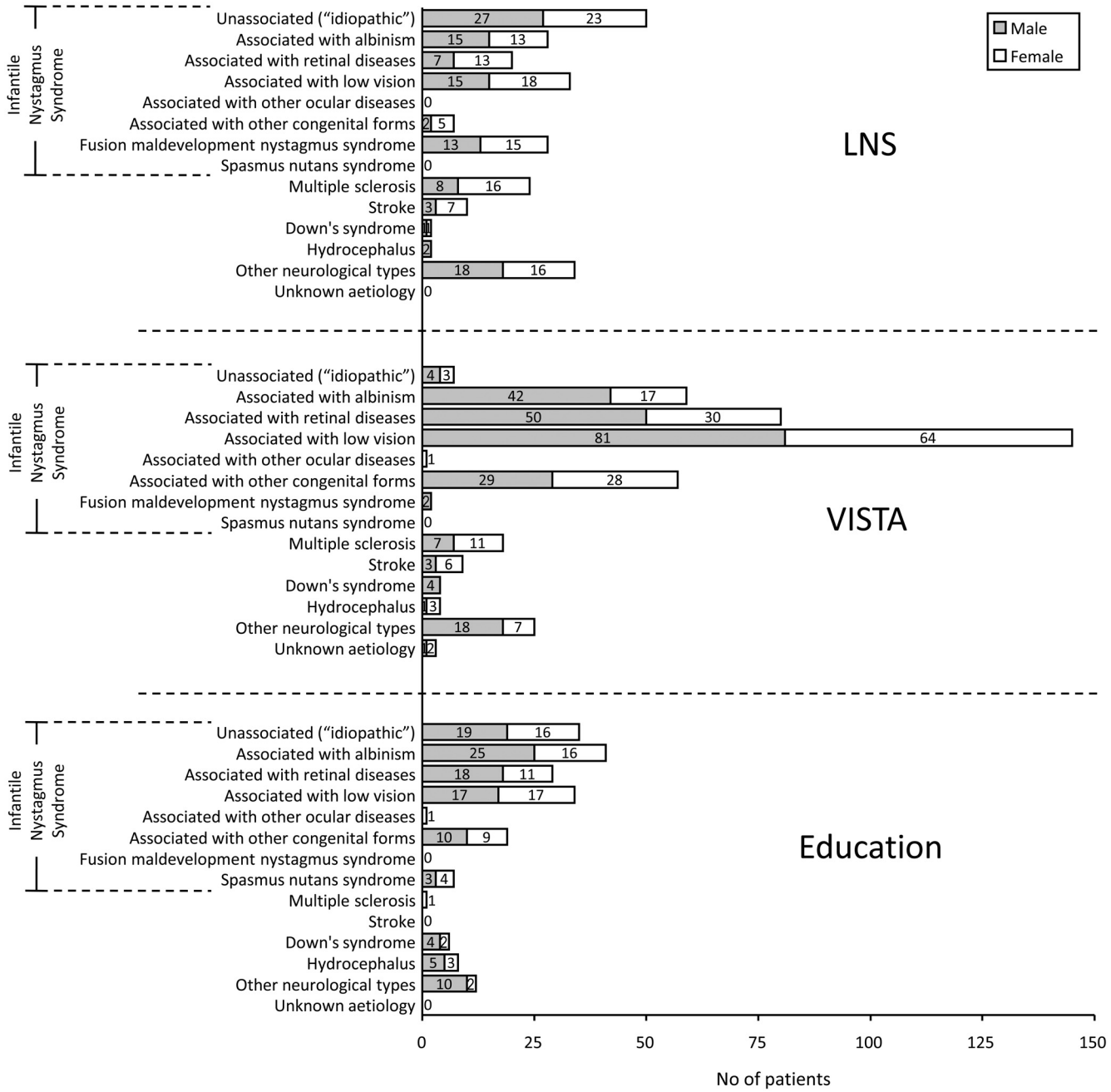

Figure 1. Bar plots representing the frequency of nystagmus forms in each of the three sources.

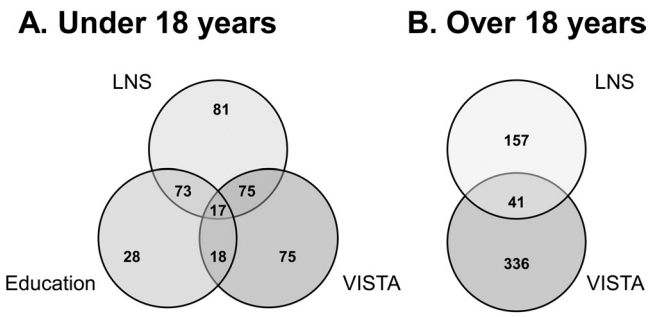

FIGURE 2. Venn diagrams of (**A**) patients 18 years of age or younger identified through one or more of three data sources. (**B**) Patients older than 18 years identified in either one or both data sources. Patients in two or more data sources are shown within the overlapping areas of the circles.

dence interval [CI], ±26). In Leicestershire 238,100 persons are 18 years of age or younger,[22] giving an estimated prevalence of nystagmus at 16.6 per 10,000 (95% CI, ±1.1) population in this age group.

In the adult (older than 18 years) age group, 1287 individuals were estimated as not captured by either data source, giving a total of 1821 (95% CI, ±473). With a population of 685,900 persons older than 18 years living in Leicestershire,[22] the prevalence of nystagmus in this age group is estimated at 26.5 per 10,000 population (95% CI, ±6.8). For the total population of Leicestershire and Rutland (925,000), the estimated prevalence of nystagmus is 24.0 per 10,000 (95% CI, ±5.3).

The clinical spectrum and frequency of patients with nystagmus were calculated separately using CRC for the 18 years of age or younger and the older than 18 groups (Fig. 3).

With CRC analysis we calculated the prevalence of the more common nystagmus-related diseases. For the total population (children and adults combined), the prevalence of unassociated INS was 1.9 per 10,000 population (95% CI, ±1.6), INS associated with albinism was 2.5 per 10,000 population (95% CI, ±0.9), INS associated with retinal diseases was 3.4 per 10,000 population (95% CI, ±2.1), INS associated with low vision was 4.2 per 10,000 population (95% CI, ±1.2), and FMNS was 0.6 per 10,000 population (95% CI, ±0.4). The total prevalence for INS was 14.0 per 10,000 population (95% CI, ±3.1; 12.0 ± 0.9 per 10,000 18 years of age or younger and 14.7 ± 3.8 per 10,000 older than 18). For neurologic nystagmus, the prevalence was 6.8 per 10,000 population (95% CI, ±4.6), with 1.9 per 10,000 population in adults attributed to multiple sclerosis and 1.5 per 10,000 population attributed to stroke. For children there was no overlap between sources for neurologic nystagmus; therefore, CRC analysis was not possible.

Sex distribution for the different forms of INS was statistically analyzed using Pearson's χ^2 test and revealed that the higher prevalence of nystagmus in males was statistically significant in INS associated with albinism ($P = 0.001$) and INS associated with retinal disease ($P = 0.048$) but not in unassociated INS ($P = 0.34$) or INS associated with low vision ($P = 0.26$)

The distribution of nystagmus from the hospital survey was compared with the distribution of the main ethnic groups obtained from the last census in Leicester city (Fig. 4). There were proportionately fewer patients with nystagmus in the Asian population (Indian, Pakistani, Bangladeshi, and a minority from other Asian backgrounds) than in the white population group (white British and other white backgrounds). Statistical analysis using Pearson's χ^2 test showed this difference to be significant ($P = 0.004$).

DISCUSSION

Our study shows the prevalence of nystagmus to be 24.0 per 10,000 population. In the 18 years or younger age group, the prevalence was 16.6 per 10,000 (95% CI, ±1.1) population, with the most common form of nystagmus attributed to INS associated with albinism. In the adult group, the prevalence was estimated to be 26.5 per 10,000 (95% CI, ±6.8) with the largest nystagmus group associated with neurologic disease.

The prevalence of nystagmus has previously been estimated only as part of larger scale epidemiologic studies into low vision[18,26–29] or among children of a specific age group, without separating congenital and acquired forms of nystagmus.[19,20] Estimates of nystagmus prevalence were 1/500,000,[17] 1/5032 among males and 1/10,596 among females,[18] 1/1000 in males and 1/2800 in females,[19] and 1/1000.[20] Although not directly comparable, the prevalence of INS in children and adults, from our study, has been found to be 14.0 per 10,000 population, which is higher than previous estimates. In terms of acquired nystagmus, although the epidemiology of multiple sclerosis is well known, the prevalence of ocular motor deficits in this condition has not been well established. The prevalence of multiple sclerosis in neighboring Cambridgeshire (latitude 52.2048 compared with latitude 52.6335 in Leicestershire) is 126 per 100,000.[30] The prevalence of nystagmus among patients with multiple sclerosis in our study was estimated to be 19 per 100 000. This is equiva-

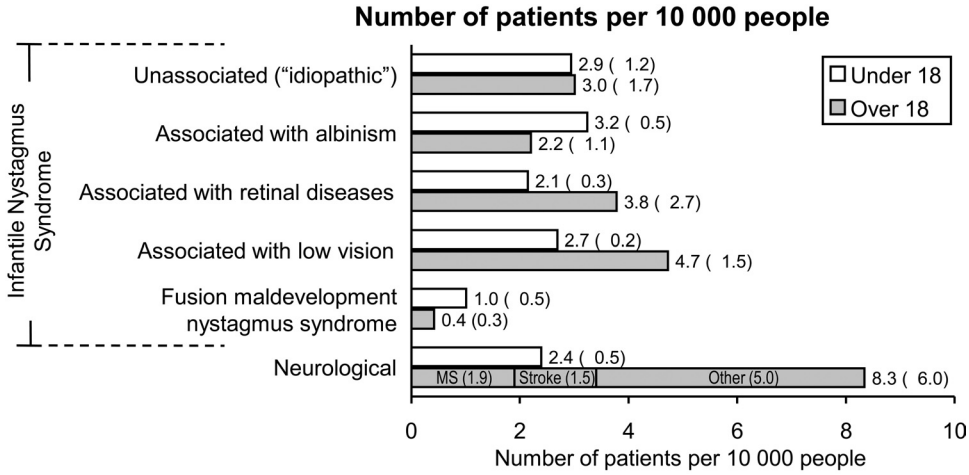

FIGURE 3. Clinical diagnosis and frequency distribution of patients with nystagmus within Leicestershire calculated by CRC statistical method. The numbers beside the bars represent prevalence per 10,000 (±95% CI), calculated separately for the 18 years or younger and older than 18 years age groups. For neurologic nystagmus forms, CRC statistics could be used only for multiple sclerosis and stroke in adults because there was no overlap between sources in children.

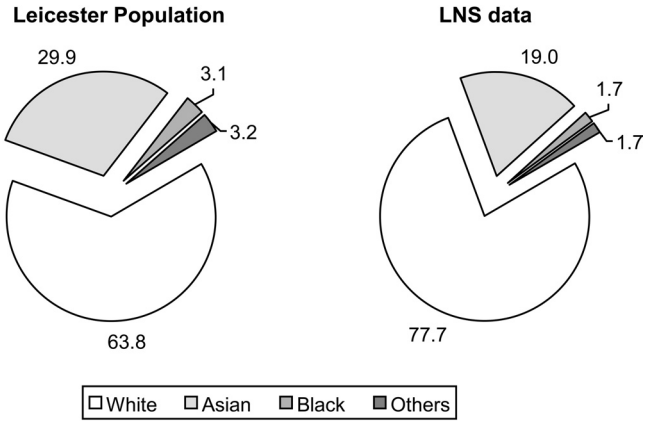

FIGURE 4. Distribution of patients with nystagmus from different ethnic backgrounds living within Leicester city compared with the city's population demographics.

lent to 15% of patients based on the Cambridge study. Although multiple sclerosis has different clinical characteristics in Japan, a study suggests that the prevalence of internuclear ophthalmoplegia in multiple sclerosis is between 17% and 41% of patients.[31]

Our study provides the first hospital-wide and community-wide estimate of the prevalence of nystagmus. It includes patients with good and poor vision who may or may not have had ophthalmic care within the hospital setting except for involvement in this study. Leicestershire has a population of 925,000 people and has a wide range of ethnic minorities (11.5%), including patients from the Asian and African subcontinents. Previous locally conducted ophthalmic research has shown that only a small number of patients obtain eye care outside the county (Deane JS, et al. *IOVS* 1998;39:ARVO Abstract 2117).[21] This epidemiologic study also enabled us to estimate for the first time the prevalence of the most common nystagmus conditions, suggesting that the most frequent form of nystagmus seen in the population is neurologic nystagmus, followed by nystagmus associated with low vision (seen in conditions such as optic nerve hypoplasia and congenital cataracts) and nystagmus associated with retinal diseases (for example, retinopathy of prematurity, achromatopsia, and congenital stationary night blindness).

The distribution of nystagmus among the various ethnic groups shows a significantly higher proportion of patients with nystagmus in the white (Caucasian) population compared with the Asian and Black ethnicity groups. Previous research into the distribution of visual impairment in children suggested a higher proportion of poor vision among the children of Pakistani heritage; 44% of the children had a family history of their ocular disease, which was attributed to the higher proportion of consanguineous marriages in this group of people.[28] However, this survey included children with different genetic ocular syndromes, and our study incorporated infantile and acquired nystagmus disorders in all age groups. It is possible that proportionately fewer Asian patients took part in our hospital survey, VISTA, and educational services because of various social reasons, such as language barriers.

CRC statistical analysis is used in epidemiology to estimate or determine the "extent of incomplete ascertainment using information from overlapping lists of cases from distinct sources."[24] The validity of CRC statistical analysis depends on several criteria being met: the cases identified from each source must have an accurate diagnosis, the study population must be closed, subjects must be randomly captured, each source must be independent from other sources, and the probability of capture in each source is equal to that for the other sources.[24,32,33] These assumptions may be difficult to prove, and complete independence of reporting sources is unlikely.[32] We ensured that the hospital and community sources of information were obtained independently and that overlapping patients were detected only at final analysis. We also ensured accurate diagnosis for all sources and closed the study population of all sources at the same date.

CRC studies have been used to estimate the prevalence of other ocular diseases, such as congenital cataract and developmental eye defects.[32,34,35] In these studies, use of independent sources of information, such as the National Congenital Anomaly Notification system (England and Wales) and independent hospital ophthalmology and pediatric surveillance schemes, showed a higher incidence of prevalence of the disease than was originally reported through passive notification.

In terms of commonality of ocular diseases, the prevalence of age-related macular degeneration (exudative and nonexudative forms) is significantly higher at 3680 per 10,000 population aged 75 or older (850 per 10,000 in those 43–54 years age),[36] whereas at the other end of the spectrum the prevalence of mitochondrial DNA defects causing diseases is 0.657 per 10,000 population.[37] Emphasis on screening and treatment have been placed on conditions such as retinopathy of prematurity, with an estimated incidence of 11.7 per 10,000 live births,[38] and congenital cataracts, with an estimated incidence of 2.49 per 10,000 children in the first year of life.[32,35] In the latter two conditions, incident figures were quoted suggesting a higher prevalence rate.[30] The results of our study suggest that similar priority should be given to detection and research into possible treatments and mechanism of nystagmus as is given to other visual impairments with comparable prevalences.

CONCLUSION

We describe the first hospital-wide and community-wide survey of the prevalence of nystagmus. Although no similar studies have been published, that the prevalence of nystagmus is higher than previously reported should alert health care providers to the need for allocation of resources for this largely under-researched condition. Our epidemiologic study has shown for the first time the prevalence of individual diseases associated with nystagmus and has highlighted the significantly higher prevalence of this condition in the white European population. The information obtained from this study emphasizes the need for more research into nystagmus, especially with emerging new understanding of pathomechanisms[15] and new treatment modalities.[3–14]

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