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Research Article

Using Large Medical Databases to Unveil Novel Disease Associations: An Example from Impaired Night Vision

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Abstract

Purpose: The co-occurrence of disease states is well recognized in clinical practice and has outstanding practical implications. In order to advance eye disease investigations, large databases may be used to unveil novel disease associations. Here, we investigate the association between impaired night vision, an uncommon disorder, and ocular and hearing disorders, using a large cohort of Israeli adolescents.

Methods: This case-control study included 662,641 Israeli adolescents that underwent medical evaluation by the Israel Defense Forces as part of the pre conscription assessment between 2005 and 2013.

Results: A total of 178 subjects (0.03%) had impaired night vision. Associations were found between impaired night vision and color blindness, non-refractive visual impairment, severe refractive error, ocular hypertension or glaucoma. We also found an association between impaired night vision and hearing loss of all types.

Conclusion: Using a large medical database, we were able to confirm previously reported disease associations and to find associations which are new, to the best of our knowledge. This study establishes the importance of using large databases to promote human health and medical research.

Keywords: *Impaired Night Vision; Night Blindness; Nyctalopia; Medical Databases; Epidemiology*

Abbreviations

RP: Retinitis Pigmentosa; CSNB: Congenital Stationary Night Blindness; FFS: Fitness-for-Service; OR: Odds Ratio; CI: Confidence Interval

Introduction

The co-occurrence of disease states is well recognized in clinical practice and has outstanding practical implications. First, the diagnosis of a disease state may warrant active search for related conditions. For example, the diagnosis of uveitis may be a first sign of a systemic disease [1] and unprovoked deep-vein thrombosis may be a sign of occult malignancy [2]. Second, the co-occurrence of diseases may signify that a common biological mechanism, either genetic or environmental, is involved in their pathogenesis. Indeed, a recent study examined the relationship between disease co-occurrence and commonly shared genetic variants to provide pathogenic insights on the biological mechanisms involved [3].

Despite the clear importance of revealing novel disease associations, several major obstacles hamper these studies. First, if a disease with low-frequency is studied, recruitment of a cohort of sufficient size is challenging. Second, if a common disease is studied, its association with rare diseases may be missed due to insufficient representation of the rare diseases in the study sample. Finally, association studies are frequently biased and look for specific associations based on previous knowledge - thus hampering the discovery of truly novel associations between apparently unrelated diseases.

To overcome the abovementioned obstacles, large databases may be used for studying multimorbidity [4,5]. As the databases include all the available medical history of patients, they can be used for non-biased search for associations between any combination of diseases. In the scope of ophthalmology, we have previously employed such an approach to unveil the association between strabismus and mental disorders in adolescents [6] and between keratoconus and allergic diseases in adolescents [7].

Here, we show the utility of this approach to advance eye disease investigations to acquire a good vision. As an example, we have investigated the association of impaired night vision (also known as night blindness or nyctalopia) with other ophthalmic conditions and with hearing loss, a non-ophthalmic condition. Impaired night vision is a symptom of retinal diseases, with retinitis pigmentosa (RP) being the most prominent cause. Additional causes include congenital stationary night blindness (CSNB), vitamin A deficiency and other uncommon etiologies [8]. Our results show association of impaired night vision with other conditions, while some of these associations have firm pathophysiological basis and others were not reported previously, to the best of our knowledge. The agreement with the previously reported associations establishes the validity of these databases for finding disease associations.

Subjects and Methods

This retrospective case-control study investigated the association between impaired night vision and several ocular disorders (color blindness, visual acuity, ocular hypertension, uveitis and scleritis), as well as with hearing loss. The study was approved by the Israel Defense Force Institutional Review Board; subject anonymity was strictly maintained.

As a part of the military preconscription assessment, most Israeli civilians undergo a routine medical and fitness-for-service (FFS) evaluation, which includes questionnaires for the candidate and his primary care physician, physical examination (including anthropometric measurements by a physician), and further tests and consultations as required. At the conclusion of this process, each candidate is assigned with FFS classification numerical codes. Each FFS is indicative of a medical diagnosis or several similar diagnoses grouped together by pathogenesis and/or functional status. The FFS codes are stored in the candidate's personal and medical record. The diagnostic criteria for the FFS codes that were used in this study are described in table 1. In addition, each candidate was assigned with a numerical code indicative of his socioeconomic status. Socioeconomic data were based on subjects' place of residence and were drawn from the Israeli Central Bureau of Statistics, which ranks all cities, towns, and villages on a composite scale of 1 (lowest) to 10 (highest).

Study Population

The study population included all Israeli teenagers that underwent medical evaluation by the Israeli defense forces as part of the pre conscription assessment between 2005 and 2013. As most of the Israeli population are conscripted by law, our database is nationwide. All subjects who underwent evaluation were included in this study, while the only exclusion criterion was age at FFS examination, excluding subjects > 16 and < 20 years of age at the time of evaluation.

Diagnosis Method

The presence of the various investigated disorders was determined in accordance with the presence of the corresponding FFS codes described in table 1.

Code	Diagnostic Criteria for FFS	Diagnostic Mechanism
Night blindness: impaired night vision	Includes retinitis pigmentosa (RP), stationary night blindness (SNB) and other moderate to severe impaired night vision	RP, SNB - diagnosis confirmed by ophthalmologist examination Other impaired night vision - Positive dark adaptation test and moderate to severe defect in electroretinography test
Color blindness	Color vision defect	Positive color vision test (Ishihara test or Farnsworth D-15 test)
Non-refractive visual impairment	Decreased visual acuity which cannot be corrected using refractive corrections	Visual acuity testing by an optometrist
Visual acuity - mild refractive error	Refractive error up to ± 6 diopters or up to 3 cylinder diopters	Visual acuity testing by an optometrist
Visual acuity - severe refractive error	Refractive error above ± 6 diopters or above 3 cylinder diopters	Visual acuity testing by an optometrist
Ocular hypertension or glaucoma	Ocular hypertension - intraocular pressure > 22 mm Hg. Glaucoma - Ocular hypertension accompanied by visual field defect.	Clinical examination by an ophthalmologist: ophthalmoscopy, applanation tonometry
Uveitis or scleritis	Inflammation of the uvea or sclera.	Visual acuity testing by an optometrist
Sensorineural hearing loss	A difference of less than 15 decibels between Air conduction and Bone conduction at each ear.	Comprehensive audiometry and clinical examination by an otolaryngologist
Conductive or mixed hearing loss	A difference of above 15 decibels between Air conduction and Bone conduction.	Comprehensive audiometry and clinical examination by an otolaryngologist

Table 1: *Diagnostic criteria of the FFS Codes in the study database.*

**FFS: Fitness-for-Service*

Statistical Analysis

Continuous variables are presented as mean with standard deviation, and categorical variables are presented as number (%) of subjects in each group. Continuous variables were compared using the independent sample t test while categorical variables were compared using a χ^2 test. A single-tailed $P < 0.05$ was considered statistically significant. All analyses were performed with the IBM SPSS Statistics V21.0.0 software (IBM Ltd., USA).

Results

Characteristics of the study population are presented in table 2. The sample included 662,641 subjects, with a male predominance (59%). A total of 178 subjects (0.03%) had impaired night vision. The socioeconomic status, body mass index and percentages of birth in Israel did not differ significantly between impaired night vision and healthy control groups.

Variable	Control	Impaired night vision	P value
Males, %	59	73.1	< 0.001
Socioeconomic status	5.86 ± 1.69	5.7 ± 1.78	0.227
Body-mass index	22.356 ± 4.1	22.38 ± 3.78	0.781
Born in Israel, %	83.3	84.25	0.735
Total number	662,463	178	

Table 2: *Characteristics of the Study Population*

Association between impaired night vision and ocular disorders

Table 3 summarizes the association between impaired night vision and other ocular disorders. The ocular disorders analysis found association between impaired night vision and color blindness (OR = 5.7; 95% CI, 3.64 - 8.9; P < 0.001), non-refractive visual impairment (OR = 24.96; 95% CI, 15.95 - 39.05; P < 0.001), severe refractive error (OR = 12.75; 95% CI, 8.81 - 18.46; P < 0.001) and ocular hypertension or glaucoma (OR = 29.01; 95% CI, 4.03 - 208.64; P = 0.034). No association was found with mild refractive error and uveitis or scleritis.

Category	Disorder	OR (Impaired night vision vs. control)	95% CI	P Value
Ocular disorders	Color Blindness	5.7	3.64 - 8.9	< 0.001
	Non-refractive visual impairment	24.96	15.95 - 39.05	< 0.001
	Visual acuity: mild refractive error	0.84	0.61 - 1.17	0.336
	Visual Acuity: severe refractive error	12.75	8.81 - 18.46	< 0.001
	Ocular hypertension or Glaucoma	29.01	4.03 - 208.64	0.034
	Uveitis or scleritis	19.09	2.66 - 136.95	0.052
Hearing Loss	Sensorineural hearing loss	5.53	2.05 - 14.9	0.007
	Conductive or mixed hearing Loss	6.21	2.3 - 16.74	0.005

Table 3: *Association between impaired night vision and ocular and hearing disorders.*

Association between impaired night vision and hearing loss

Table 3 summarizes the association between impaired night vision and hearing loss. This analysis found a significant association between impaired night vision and both Sensorineural hearing loss (OR = 5.53; 95% CI, 2.05 - 14.9; P = 0.007) and conductive or mixed hearing loss (OR = 6.21; 95% CI, 2.3 - 16.74; P = 0.005).

Discussion

The scope of the current special issue, "*Eye Diseases and Their Investigations to Acquire a Good Vision*", is of utmost important for researchers and clinicians in the field of ophthalmology. The purpose of the current study was to demonstrate the utility of using large medical databases to promote ophthalmic research.

Here, we investigated the association of a relatively uncommon disorder - impaired night vision - with various disorders using a large national database of Israeli adolescents. Using this large cohort, we were able to reinforce previously reported associations and to find novel associations that may guides future pathophysiological research.

Our analysis reinforced the previously described association between impaired night vision and decreased visual acuity, either due to severe refractive error [9] or non-refractive visual impairment (e.g., in retinitis pigmentosa [10]). In addition, our study found an

association between impaired night vision and color blindness - both known to co-occur in CSNB [11] and advanced RP [10]: Previous color vision abnormality is an initial presentation of the complete type of congenital stationary night blindness [11], and deficiency in blue cone function is characteristic of advanced RP [10]. This is a sound example for disease co-occurrence implicating a common biological mechanism [3].

Finally, we were also able to demonstrate an association between impaired night vision and hearing loss of all types. This is intriguing, as although the association between impaired night vision and sensorineural hearing loss is a feature of Usher syndrome and Refsum disease [12,13], the association of impaired night vision with conductive or mixed hearing loss was not previously demonstrated, to the best of our knowledge.

Another interesting association found in this study is between impaired night vision and ocular hypertension or glaucoma. Previously, a small study showed that night visual function decreases with the progression of glaucoma and the rise of ocular hypertension [14]. Whether glaucoma hampers night vision or impaired night vision is a predisposing factor for glaucoma remains to be determined.

Conclusion

Using a large medical database, we were able to confirm previously reported disease associations and to find associations which are new, to the best of our knowledge. This study establishes the importance of using large databases to promote human health and medical research.

Authors Contribution

Dr. Gilad Winder and Dr. Ayal Hassidim have contributed equally for this manuscript.

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