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Prevalence and associated relating factors in patients with hereditary retinal dystrophy: a nationwide population-based study in Taiwan

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ABSTRACT

Objective To investigate the prevalence, incidence and relating factors that are associated with hereditary retinal dystrophy (HRD) in Taiwan from 2000 to 2013.

Design, setting and participants This is a nationwide, population-based, retrospective case–control study using National Health Insurance Database. Study groups are patients with HRD as case group; age-matched patients without any diagnosis of HRD as control group. We enrolled 2418 study subjects, of which 403 were HRD patients. Important relating factors such as hypertension, diabetes, coronary artery disease, autoimmune disease, cancer, liver cirrhosis, chronic kidney disease, stroke, hyperlipidaemia, asthma, depression and dementia are also included.

Exposure Patients diagnosed with HRD were retrieved from National Health Insurance Database.

Main outcomes and measures OR calculated between the relating factors and HRD for objects and stratified by age and sex group between 2000 and 2013.

Results Four hundred and three patients were included in the study group and 2015 in the control group. The incidence of HRD was 3.29/100 000, and the prevalence of HRD was 40.5/100 000 persons. The tendency of study group to have more cataract, cystoid macula oedema (CME) as compared with the control group. Among the subgroup with comorbidities, the relating factors such as hypertension, diabetes and chronic kidney disease was significantly higher among HRD patients with age 55 and above.

Conclusions 74% of the diagnosed HRD are retinitis pigmentosa. Population-based data suggested an increased incidence of cataract in younger patients, whereas older HRD patients are more susceptible to develop CME. Further work is needed to elucidate the mechanism between these ophthalmological disorders and HRD.

Strengths and limitation of this study

- A nationwide, population-based study was conducted to explore the prevalence, incidence and relating factors associated with hereditary retinal dystrophy in Taiwan.
- The Taiwan National Health Insurance Database provides over 20 years of comprehensive and detailed registry and claims data covering over 23 million of Taiwan's population.
- Comprehensive details on regional and country-wide hospitalisation, healthcare utilisation, disease diagnoses, vaccinations, surgical procedures and medications of every individual.
- This study takes into account of major relating factors and other covariates.
- The risk of misclassification bias on certain disease phenotypes or diseases identifications may not be completely excluded.

INTRODUCTION

Hereditary retinal dystrophies (HRD), such as retinitis pigmentosa (RP), cone dystrophy, Stargardt disease, Usher syndrome, Leber's congenital amaurosis, retinoschisis, etc, are a group of genetic retinal disorders exhibiting both genetic and phenotypic heterogeneity with a collectively estimated incidence of 1:2000–1:3000.[1–3] Among HRD, RP, one of the most common forms with variable clinical manifestations, affects approximately 1 in 3000–4000 people worldwide.[4 5]

To date, there is more than 271 genes (Retnet: https://sph.uth.edu/retnet/, last update 21 January 2021) associated with HRD have been identified. The clinical manifestations of HRD patients may vary according to complexity of the genetic background and most common features include night blindness, constricted visual field, colour vision deficiency or even total blindness. The other ocular complications, such as cataract, cystoid macular oedema (CME) or epiretinal membrane, will further deteriorate central vision and increase activity limitation at younger age. A wide range prevalence of these complications in HRD has been reported in different studies. Accurate assessment will help to identify these complications and foster the development of advanced therapeutic approaches.

The aim of this study is to explore the prevalence and relating factors that are associated with HRD in a nationwide, population-based, retrospective case–control study using Taiwan National Health Insurance (NHI) Database. The NHI database was used to retrieve cases of HRD to investigate the events of cataract, CME, epiretinal membrane, retinoschisis and other covariates.

MATERIALS AND METHODS

Data source

This was a nationwide population-based retrospective case–control study. The NHI programme, which was implemented in Taiwan on 1 March 1995, constructed a high coverage health database, named National Health Insurance Database (NHIRD) and enrolled over 99% of population in Taiwan as of today. The records of outpatients, hospitalisation, medical treatment and other medical services of each hospital visit were included in the database. We conducted the analysis by using Longitudinal Health Insurance Database 2000 (LHID 2000), the subset of NHIRD. LHID 2000 consisted of 1 million study subjects, which was randomly sampled from NHIRD and made sure they were already insured in the year 2000. The database was merely for medical research and the identification numbers of all individuals were encrypted to protect the privacy of the individuals. The diagnoses in Taiwan NHIRD are defined according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM).

Study subjects

We identified 403 subjects from the LHID2000 with the diagnosis of HRD (ICD-9-CM Code 362.7x) made between 1 January 2000 and 31 December 2013. The index date for a HRD subject was the date when the disease was first coded.

Control group

Control patients were defined as subjects without any diagnosis of HRD and were pair matched to the subjects with HRD by age, sex and index date in a ratio of 5 controls to each HRD subject.

Relating factors and other covariates

The relating factors included cataract (ICD-9: 366.X or Pseudophakia (V43.1) or procedure code: 86 007C, 86 008C, 86 009C, 86 010B), CME (ICD-9: 362.53), retinoschisis (ICD-9:361.1), epiretinal membrane (ICD-9: 362.56), retinal detachment (ICD-9: 361.0), and YAG capsulotomy (procedure code: 60 013C, 60 014C), which had diagnosis record within 1 year before the index date. Some comorbidities were included as other covariates. These comorbidities were important relating factors in this study. We defined the comorbidities occurred 1 year before the index date and with at least twice outpatients or once hospitalisation record. Hypertension (ICD-9: 401–405, A260, A269), diabetes (ICD-9: 250, A181), coronary artery disease (ICD-9: 410–414, A270, A279), autoimmune disease (ICD-9: 710, 714), cancer (ICD-9: 140–208), liver cirrhosis (ICD-9: 571.2, 571.5, 571.6), chronic kidney disease (ICD-9: 582, 583, 585, 586, 588), stroke (ICD-9: 430–438), hyperlipidaemia (ICD-9: 272, A182), asthma (ICD-9: 493), depression (ICD-9: 296.2, 296.3, 296.82, 300.4, 309.0, 309.1, 309.28, 311) and dementia (ICD-9: 290, 294.1, 331.0) were also included.

Statistical analysis

The annual incidence rate of HRD was calculated by the annual newly diagnosed HRD patients divided by every 100 000 person-year. The difference of demographic and comorbidities between two groups was compared by χ^2/Fisher's exact test and t-test for categorical and continuous variable, respectively, and the variants/factors of HRD was evaluated by conditional logistic regression and shown by OR, adjusted OR (aOR) and 95% CI. All statistical analyses were carried out using Statistical Analysis Software (SAS), V.9.4 (SAS Institute). The significant criteria set at two-sided p<0.05.

Patient and public involvement

No patient involved.

RESULTS

HRD incidence

Figure 1 presents the annual incidence rate of HRD from 2000 to 2013. The incidence rate of HRD showed approximately 2.62–4.55 every 100 000 person-year, with an average rate of approximately 3.29 every 100 000 person-year in Taiwan. The annual incidence rate was consistent during the 14 years follow-up.

Demographics

Figure 2 presents the demographic, relating factors and comorbidities of study subjects. In total, we enrolled 2418 study subjects, including 403 HRD patients and 2015 non-HRD patients, and the mean age was 49 years old. After comparing the prevalence of relating factors and between HRD and non-HRD group, HRD patients showed significant higher prevalence of cataract (p<0.001), CME (p<0.001), posterior capsulotomy (p=0.035), hypertension (p=0.016), diabetes (p<0.001), chronic kidney disease (p=0.013) and hyperlipidaemia than non-HRD patients. RP accounted for 74% of HRD diagnosis.

Factors associated with HRD

Figure 3 reveals the crude and aOR of having HRD for subjects with or without some ocular diseases or comorbidity with the adjustment for age, sex and comorbid diseases. Patients with HRD were significantly associated with cataract (aOR 6.03, 95% CI 3.60 to 10.10) and CME (aOR 14.64, 95% CI 6.78 to 31.60), but not with epiretinal membrane, retinal detachment, depression or dementia. The development of CME in HRD patients is correlated to age. The prevalence rate of CME in HRD

Year	HRD	Total Population Person Years	Annual Incidence Rate per 100,000 person years
2000	42	922354	4.55
2001	29	918184	3.16
2002	33	903289	3.65
2003	28	893619	3.13
2004	34	887334	3.83
2005	28	881009	3.18
2006	29	874763	3.32
2007	29	868228	3.34
2008	26	861413	3.02
2009	24	854379	2.81
2010	24	854379	2.81
2011	22	839714	2.62
2012	30	831452	3.61
2013	25	819168	3.05

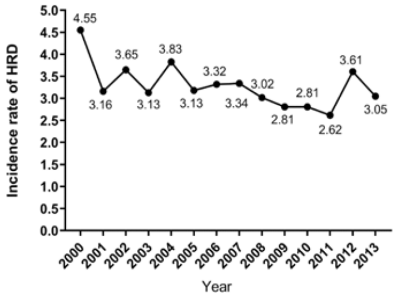

Figure 1 Incidence of HRD from 2000 to 2013. HRD, hereditary retinal dystrophies.

patients older than 55 years (9.4%) is higher than the HRD patients below 55 years of age (4.5%).

Stratification analysis

Figure 4A,B shows the characteristics of patients with or without HRD stratified by age. Among subjects who were older than 55 years, HRD group had significant higher prevalence of cataract (p=0.002), CME (p<0.001), diabetes (p<0.001) and hyperlipidaemia (p=0.028). Similarly, HRD group had significant higher prevalence of cataract (p<0.001), CME (p<0.001), posterior capsulotomy (p=0.005), hypertension (p=0.001), diabetes (p=0.035) and chronic kidney disease (p=0.017) among subjects who younger than 55 years old.

After stratification by age and gender, patients who were male (aOR 7.00, 95% CI 3.37 to 14.54), female (aOR 5.22, 95% CI 2.47 to 11.05), younger (aOR 22.01, 95% CI 7.86 to 61.65) or older than 55 years (aOR 3.08, 95% CI 1.55 to 6.11) with cataract showed significant association with HRD, aOR was higher especially among patients younger than 55 years old. CME also showed significant association with HRD among male (aOR 14.89, 95% CI 5.21 to 42.60), female (aOR 14.77, 95% CI 4.73 to 46.06) and patients who are older than 55 years (aOR 8.07, 95% CI 3.43 to 19.03).

DISCUSSIONS

In this retrospective case–control study using NHI database, the prevalence of cataract, CME, epiretinal membrane, retinal detachment and retinoschisis in HRD patients (n=403) was 8.2%, 6.5%, 0.5%, 0.5% and 0.3%, respectively. Compared with individuals without HRD, patients with HRD had a higher incidence of cataract (8.2% vs 1.5%, p<0.001) and CME (6.5% vs 0.5 %, p<0.001) and HRD patients aged younger than 55 years had an increased risk of hypertension, diabetes and chronic kidney disease. These data indicate the prevalence of potentially treatable HRD related ocular complications is relatively high and the comorbidities are more likely to develop at younger HRD patients.

The reported prevalence of CME in patient with HRD especially RP ranges from 14% to 23% as evaluated by fluorescein angiography (FA),[6–8] 7.5% to 49% as evaluated by time domain-optical coherence tomography OCT (TD-OCT)[9–12] and 12.5% to 58.6%[13–18] as evaluated by spectral domain OCT. However, these reports mostly were single-hospital study and were non-population-based data which cannot be used to calculate the exact prevalence rate of CME. Our prevalence for CME (6.5%) is relatively lower than the previous reports but similar to the studies by Oishi *et al*,[11] detected CME in 49 eyes (7.5%) out of 652 eyes of 326 patients and Hagiwara *et al*[19], reported CME was detected in 26 (8%) out of 323 patients with RP using TD-OCT. The big discrepancy in CME prevalence rate among the studies may associated with different definition of CME, different detection methods and equipment or different populations. The exact aetiology of CME in HRD remains uncertain and various proposed pathophysiological mechanisms, such as breakdown of the blood–retinal barrier,[20 21] Muller cell dysfunction,[22] vitreomacular traction,[23 24] antiretinal autoantibodies[25] and retinal pigment epithelium dysfunction,[26] have been suggested.[27 28] Additionally, further investigation to evaluate the association between CME and the genetic background effects will also be needed.

Patients with HRD tend to develop cataract at younger age as compared with general population. Posterior subcapsular cataract is the most common form of cataract observed in patients with HRD, whereas nuclear or cortical cataract is more common in age-related cataract.

	Total	Non-HRD	HRD	p-value
	N=2418	(n=2015)	(n=403)	
	n	n (%) / mean(SD)	n (%) / mean(SD)	
Gender				1.000
Female	1242	1035 (51.4)	207 (51.4)	
Male	1176	980 (48.6)	196 (48.6)	
Age, years				1.000
<20	210	175 (8.68)	35 (8.68)	
20-39	552	460 (22.83)	92 (22.83)	
40-59	876	730 (36.23)	146 (36.23)	
≥60	780	650 (32.26)	130 (32.26)	
mean(SD)[a]		49.1 (18.7)	49.2 (18.6)	0.939
Risk factors				
Cataract	64	31 (1.5)	33 (8.2)	<0.001
Macular edema	35	9 (0.5)	26 (6.5)	<0.001
Retinal detachment[b]	4	2 (0.1)	2 (0.5)	0.132
Retinoschisis[b]	1	0 (0.0)	1 (0.3)	0.167
Posterior Capsulotomy	13	8 (0.4)	5 (1.2)	0.035
Epiretinal membrance[b]	3	1 (0.1)	2 (0.5)	0.074
Comorbidity				
Hypertension	471	375 (18.6)	96 (23.8)	0.016
Diabetes	241	176 (8.7)	65 (16.1)	<0.001
Coronary artery disease	127	101 (5)	26 (6.5)	0.237
Autoimmune diseases[b]	1	0 (0)	1 (0.2)	0.167
Malignancies	13	12 (0.6)	1 (0.2)	0.384
Liver cirrhosis	10	9 (0.4)	1 (0.2)	0.571
Chronic kidney disease	34	23 (1.1)	11 (2.7)	0.013
Cerebrovascular disease	98	87 (4.3)	11 (2.7)	0.140
Hyperlipidemia	228	176 (8.7)	52 (12.9)	0.009
Asthma	56	45 (2.2)	11 (2.7)	0.545
Depression	49	38 (1.89)	11 (2.73)	0.273
Dementia	25	22 (1.09)	3 (0.74)	0.529
Retinitis Pigmentosa, RP		-	300 (74.4)	

[a]t-test

[b]Fisher exact test

Figure 2 Characteristics of patients with or without HRD. HRD, hereditary retinal dystrophies.

The severity of cataract in HRD patients is related to the onset age and the duration of disease progression. In Taiwan, the prevalence rate of cataract surgery was 0.54% and the incidence rate of first cataract surgery was 0.44% in 2010.[29] Data from previous reports indicated that women had higher incidence rate of cataract surgery.[29–33] In this study, the prevalence rate of cataract surgery is significantly higher in HRD patients compared with age-matched non-HRD people (8.3% vs 1.3%; p<0.001). aOR of cataract in HRD patients younger than 55 years and older than 55 years is 22.01 (95% CI 7.86 to 61.65) and 3.05 (95% CI 1.55 to 6.11), respectively. Our results suggest that cataract occurred at younger age and more frequently among man than among women in HRD patients.

In this study, HRD subjects younger than 55 years had a higher prevalence of hypertension, diabetes and chronic kidney diseases than the age-matched control subjects while HRD subjects older than 55 years had a higher prevalence of diabetes and hyperlipidaemia than the age-matched control subject. The association between these comorbidities and HRD is unclear. Some individuals with HRD may have other associated non-ocular diseases.[2 34] Patients with Bardet-Biedl syndrome (BBS),[35 36] Alstrom syndrome (AS),[37 38] Kearns-Sayre syndrome[39 40] and Wolfram syndrome,[41 42] have been reported to have the combination of diabetes and retinal dystrophy. BBS and AS patients usually show the symptoms of obesity and impaired renal function while Senior-Loken syndrome patients are not obese but present

Characteristics	OR (95% CI)	p value	aOR (95% CI)	p value
Cataract				
No	Ref.		Ref.	
Yes	5.68 (3.44-9.40)	<0.001	6.03 (3.60-10.10)	<0.001
Macular edema				
No	Ref.		Ref.	
Yes	14.68 (6.86-31.41)	<0.001	14.64 (6.78-31.60)	<0.001
Retinal detachment				
No	Ref.		Ref.	
Yes	5.00 (0.70-35.50)	0.108	5.15 (0.71-37.38)	0.105
Retinoschisis				
No	Ref.		Ref.	
Yes	-	-	-	-
Posterior Capsulotomy				
No	Ref.		Ref.	
Yes	3.17 (1.03-9.79)	0.045	2.96 (0.90-9.74)	0.074
Epiretinal membrance				
No	Ref.		Ref.	
Yes	8.39 (0.74-94.51)	0.085	-	-
Depression				
No	Ref.		Ref.	
Yes	1.46 (0.74-2.88)	0.276	1.31 (0.65-2.63)	0.449
Dementia				
No	Ref.		Ref.	
Yes	0.65 (0.18-2.31)	0.509	0.76(0.20-2.91)	0.689

Abbreviation: OR, odds ratio; CI, confidence interval

Figure 3 ORs and 95% CIs of HRD associated with eye diseases and comorbidities. HRD, hereditary retinal dystrophies.

with severe renal dysfunction.[43 44] Several reports have suggested that patients with RP may lower their risk of developing proliferative diabetic retinopathy (PDR). Reducing retinal metabolism may be associated with decreased retina oxygen demand and retinal hypoxia resulting in ameliorating diabetic retinopathy.[45 46] Although RP might lack the risk of PDR, the vasoregression in an early stage of diabetic retinopathy and PDR indicated that increased ROS, VEGF and angiopoietin-2 might induce the progressive degeneration of the blood vessels.[47] The vasoregression of the pathophysiological process between diabetic retinopathy in the early stage is similar to RP, suggesting diabetic retinopathy might be enhanced the process of RP.[48] Furthermore, patients have RP with diabetic retinopathy have been observed in case reports.[49–51] The pathophysiological mechanisms underlying the high prevalence of these comorbidities in HRD patients are worth further investigation.

A

	Total	Non-HRD	HRD	p-value
	n	n (%)	n (%)	
Age, ≥55 years				
Risk factors				
Cataract	40	26 (3.2)	14 (8.7)	0.002
Macular edema	24	9 (1.1)	15 (9.3)	<0.001
Retinal detachment	0	0 (0.0)	0 (0.0)	-
Retinoschisis	3	2 (0.2)	1 (0.6)	0.422
Posterior Capsulotomy	10	8 (1)	2 (1.2)	0.676
Epiretinal membrance	2	0 (0.0)	2 (0.8)	0.028
Comorbidity				
Hypertension	373	305 (37.9)	68 (42.2)	0.301
Diabetes	190	139 (17.3)	51 (31.7)	<0.001
Chronic kidney disease	27	20 (2.5)	7 (4.3)	0.190
Hyperlipidemia	170	132 (16.4)	38 (23.6)	0.028

B

	Total	Non-HRD	HRD	p-value
	n	n (%)	n (%)	
Age, <55 years				
Risk factors				
Cataract	24	5 (0.4)	19 (7.9)	<0.001
Macular edema	11	0 (0.0)	11 (4.5)	<0.001
Retinal detachment	1	0 (0.0)	1 (0.4)	0.167
Retinoschisis	1	0 (0.0)	1 (0.4)	0.167
Posterior Capsulotomy	3	0 (0.0)	3 (1.2)	0.005
Epiretinal membrance	1	1 (0.1)	0 (0.0)	1.000
Comorbidity				
Hypertension	98	70 (5.8)	28 (11.6)	0.001
Diabetes	51	37 (3.1)	14 (5.8)	0.035
Chronic kidney disease	7	3 (0.2)	4 (1.7)	0.017
Hyperlipidemia	58	44 (3.6)	14 (5.8)	0.119

Figure 4 (A) Characteristics of patients older than 55 years old with or without HRD. (B) Characteristics of patients younger than 55 years old with or without HRD. HRD, hereditary retinal dystrophies.

Chen *et al*, reported that patients with certain phenotypes such as Leber congenital amaurosis, retinoschisis, familial exudative vitreoretinopathy and AS displayed retinal dystrophies earlier in life,[52] and probands with ABCA4, RPGR, RP1L1 and CEP290 mutations sought medical attention at a significantly very young age (age onset 0.89–4.00 years old). As ABCA4 was the single most common disease-causing gene in their cohort (15.2%), echoed the data published from the US cohort (17.3%). Consequently, it would be worth further investigation if HRD patients in our study exhibit the similar event. Of noted, the age onset of our cohort was much older (mean 49.2 years old, figure 2). They also observed that patients with RP, macular dystrophy and Bietti crystalline dystrophy occurred at much older age (age onset ranged from 29.42 to 36.64).[52] Unfortunately, other relating factors such as hypertension, diabetes, chronic kidney disease and hyperlipidaemia did not receive much attention from Chen *et al*. Perhaps worth mentioned was that on average, their cohort had an age-onset much younger (mean age onset of 28.17 years old) as compared with the Taiwan IRD population. The HRD age of onset of our cohort (mean 49.2 years old, figure 2) closed to the national record, which made our study unique and truly represented.

The central vision of HRD patients may be compromised not only by primary disease process but also by the complications occurring as the diseases progresses. CME and cataract are the main relating factors of central visual deteriorating in patients with HRD. Those complications may be solved with surgery or medication, resulting in improved anatomical and visual outcomes. The putative environmental factors may also contribute to these comorbidities. It has been reported that environmental enrichment can enhance the survival of photoreceptors in a mouse model. This phenomenon is similar to the environmental enrichment that can stimulate the visual cortex. Patients with RP lack physical functioning and increase depression in life.[53] Lack of physical activity enhances the relative contributions of comorbidities and HRD. Increasing physical activity can be effective in obesity reduction of oxidant stress. Those factors might affect the comorbidities and HRD.[54 55] To encourage the patients to explore the environment, physical exercise and cognitive stimulation might delay retinal degeneration.[56]

LIMITATIONS

This case–control retrospective study has limitations. First, the NHI database does not provide information regarding personal physical activity, nutrition, lifestyles, body mass index or metabolic profiles affecting the risks of hypertension, hyperlipidaemia, diabetes and chronic kidney diseases. Second, the ICD-9-CM codes for the diagnosis of HRD and the comorbid diseases were less precise than the data collected through standardised clinical examination. Furthermore, there is no specific code for each different HRD, such as cone-rod dystrophy, Stargardt diseases, Usher syndrome, Leber's congenital amaurosis and other retinal dystrophy associated syndromes. Third, we may have underestimated the prevalence of CME in HRD subjects since there was no standard criteria to define CME on OCT sans from the NHI database.

CONCLUSIONS

These finding from our nationwide, population-based case control study suggests an increased risk of cataract in younger HRD patients, whereas older HRD patients are more susceptible to develop CME. Understanding the pathophysiological mechanisms between these ocular complications and HRD will help to develop effective therapies to improve patients' vision. Furthermore, younger HRD patients have a higher tendency to develop hypertension, diabetes and chronic kidney diseases. We recommended that regular screening and monitoring of HRD patients with OCT, blood pressure, levels of electrolytes and serum glucose levels may beneficial for early intervention of patients with HRD and may help to maintain central vision and may prevent vascular, metabolic and renal comorbidities.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115-R4).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information. All data relevant to the study are included in the article.

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