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Inherited retinal dystrophies caused by *RPE65* gene mutation: clinical presentation, economic and social burden

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ABSTRACT

Inherited retinal dystrophies are a heterogeneous group of genetically determined disorders. The present paper discusses the role of mutation in the gene encoding the retinal pigment epithelium-specific protein RPE65 in the pathogenesis and course of dystrophies. Available epidemiological data are discussed with a focus on the clinical entities in which the *RPE65* mutation is most typically identified, i.e. retinitis pigmentosa and Leber congenital amaurosis. As demonstrated by multiple studies, the lack of active retinal pigment epithelium-specific protein leads to near-total vision loss already in childhood or early adolescence.

The paper addresses the issue of economic burdens associated with visual disturbances or vision loss resulting from progressive visual dysfunction, including the burden on the healthcare system and public payer, and relating to the loss of productivity (indirect costs). In addition, an attempt has been made to evaluate the latter in the Polish reality. Unquantifiable costs, understood as referring to the loss of quality of life caused by progressive visual dysfunction, are discussed from the perspective of both patients and their caregivers.

KEY WORDS: inherited retinal dystrophies, *RPE65*, disease costs, direct costs, indirect costs, quality of life

INTRODUCTION

Inherited retinal dystrophies (IRD) are a group of etiologically and clinically heterogeneous diseases with a genetic background. They can affect the central part of the retina (macular dystrophies) or the peripheral retina, but in its advanced form, the disease involves the entire retinal area. In addition, dystrophies can be classified depending on the photoreceptor affected (into rod, cone, or cone-rod types), manifestations of the disease, or the degree of retinal atrophy. Some forms of IRD are known to coexist with other disorders, such as deafness in Usher syndrome or obesity, cognitive dysfunctions, polydactyly, hypogonadism, and kidney disease in Bardet-Biedl syndrome [1, 2].

The clinical picture is characterized by progressive reduction in the visual field range and/or deterioration of visual acuity. Depending on the type of dystrophy and the underlying mutation, the course of the disease may vary from mild forms, with patients retaining useful visual acuity up to 50–60 years of age, to severe variants leading to blindness in early childhood [3]. By the end of June 2020, over 270 genes whose mutation causes various forms of retinal dystrophy had been identified. The genes encode proteins responsible for the normal functioning of photoreceptors, retinal pigment epithelium, and other retinal cells [1, 4].

RPE65 gene mutation in the pathogenesis of retinal dystrophies

One of the well-studied genes the mutation of which leads to retinal dystrophy is the gene encoding the retinal pigment epithelium 65 kDa protein (RPE65 protein) which is present in the retinal pigment epithelium (RPE). The enzyme RPE65 (isomerhydrolase) is responsible for converting all-trans-retinol to the cis form in the visual cycle. Thus, it plays a key role in the regeneration of visual pigment and its return to photoreceptor cells [5]. A mutation in the *RPE65* gene causes a deficiency of the active enzyme, resulting in the accumulation of visual cycle products in the pigment epithelium and impaired light response ability of photoreceptor cells. Ulti-

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mately, the process leads to the death of RPE cells and, as a consequence, the death of photoreceptor cells as well [6, 7]. Patients are found to have diverse types of mutations in the *RPE65* gene. Furthermore, there is a high degree of variation in visual impairment between individuals with the same type of mutation. Central vision in childhood is affected to varying levels and may remain stable during the first three decades of life. The progressive nature of the disease, however, inevitably leads to blindness [8].

Natural progression of retinal dystrophies with *RPE65* mutation

The diversity of clinical presentations of IRD and varying severity of symptoms observed in patients with the *RPE65* mutation leads to a wide range of diagnoses [8]. If the first manifestations of the disease are related to the degeneration of rod cells and develop between the ages of 5 and 30, patients are most commonly diagnosed with *retinitis pigmentosa* (RP). The first symptom reported by patients is impaired mesopic vision, occasionally accompanied by decreased peripheral vision. As the disease advances, the cone cells, which are critical for visual acuity and color discrimination, also become affected. The disease gradually progresses to severe visual disturbances or complete blindness due to loss of central vision [7, 9]. In another type of disease, with an early onset and more rapid progression, Leber congenital amaurosis (LCA) is most commonly diagnosed. In patients with LCA, the dystrophy affects both rods and cones, with symptoms appearing immediately after birth. Affected children experience severe visual disturbances or blindness which can develop as early as by 6 months of age [8, 10].

Regardless of the clinical diagnosis, the biallelic *RPE65* mutation causes a loss of light perception as the disease progresses. As the patients age, their visual acuity deteriorates and the field of vision is reduced, and structural changes develop within the lens, macular retina, optic disc, and retinal blood vessels. From about 14 to 15 years of age, severe visual impairment is diagnosed according to the criteria adopted by the International Council of Ophthalmology (ICO). By the age of 18, more than half of patients meet the U.S. legal criteria for blindness [8, 11].

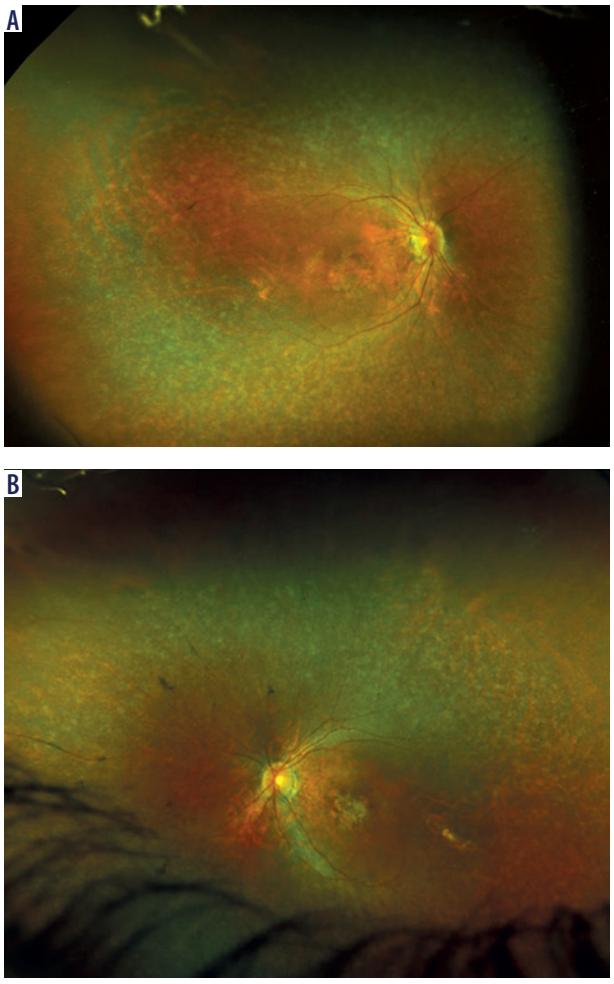

Figure 1. Slit-lamp fundus photograph in a 10-year-old boy with biallelic *RPE65* gene mutation

Case report of patient with LCA and biallelic *RPE65* gene mutation

A 10-year-old boy with a genetically confirmed biallelic homozygous *RPE65* mutation (*RPE65* c.1451G>T) presented with significant deterioration of visual acuity, impaired mesopic vision, narrowing of the visual field, and nystagmus since the age of 5 months. Visual acuity in the right eye was determined as hand motion, and in the left eye it was assessed as 1/50. The intraocular pressure was normal bilaterally. On slit-lamp examination, the anterior segment appeared normal, with no abnormalities seen in the vitreous. The fundus revealed multiple fine-spotted atrophic changes, macular retinal atrophy, vascular attenuation, and pale optic nerve disc (Figure 1). Horizontal retinal scans obtained by spectral-domain optical coherence tomography (SD-OCT) revealed areas of significant photoreceptor atrophy and thinning of the outer retinal layers as well as increased signal penetration into the choroid due to defects in the RPE layer (Figure 2). In view of the deficiency in the production of RPE65 protein, the natural course of the disease is expected to lead to further progression of symptoms and deterioration of visual parameters.

EPIDEMIOLOGY

Data on the epidemiology of IRD caused by the *RPE65* mutation as a sole disease entity are limited and usually encompass a variety of clinical diagnoses. As reported by Chung *et al*, patients with a biallelic mutation of the *RPE65* gene undergo diagnostic work-up for suspected LCA (approximately 50% of cases) or RP (8%) at their first clinical visit. Both LCA and RP are classified as rare diseases [12].

Retinitis pigmentosa (RP) is included among the most common forms of IRD [13]. Studies conducted across Europe show that the prevalence of RP in different countries ranges from about 1/8.3 thousand in Spain [14] to 1/3.9 thousand in Denmark [15]. RP is seen predominantly among individuals over the age of 65 [16]. The prevalence of *RPE65* mutations

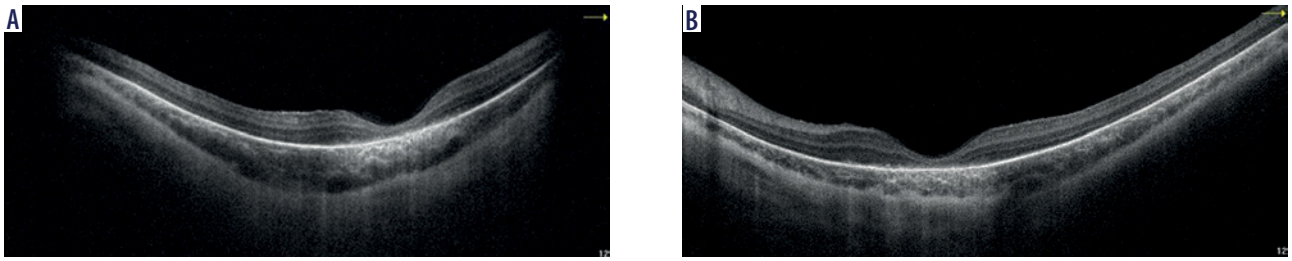

Figure 2. Horizontal SD-OCT retinal scans in a 10-year-old boy with biallelic *RPE65* gene mutation

Table I. Frequency of diagnosis of *RPE65* gene mutations among patients with Leber congenital amaurosis (LCA) and retinitis pigmentosa (RP) in studies conducted across Europe

Country	Leber congenital amaurosis		Retinitis pigmentosa	
	Percentage of cases with *RPE65* gene mutation	Source	Percentage of cases with *RPE65* gene mutation	Source
Germany	1,8%	Eisenberger 2013 [21]	0,0%	Eisenberger 2013 [21]
Spain	2,4%	Vallespin 2007 [22]	–	
UK	3,4%	Henderson 2007 [23]	0,8%	Wang 2014 [13]
Netherlands	6,7–22,2%	Haer-Wigman 2017 [18], Booij 2005 [27]	1,6%	Haer-Wigman 2017 [18]
Italy	8,4%	Simonelli 2007 [24]	–	
Belgium	8,8%	Coppieters 2010 [25]	–	
France	16,0%	Bocquet 2013 [17]	1,1%	Bocquet 2013 [17]
Denmark	17,4%	Astuti 2016 [26]	–	–
Mean	9,7%		0,9%	

in the European population of patients with RP has been reported to range from approximately 1% in France [17] to 1.6% in the Netherlands [18] (table I).

Leber congenital amaurosis is a rare genetic disorder with a prevalence estimated at between 1/81,000 of the population in the United States [19] to 1/42,000 in Denmark [20]. The percentage of LCA patients with the *RPE65* mutation varies significantly depending on the region of study. In Europe, it has been found to range from 2% in Germany to 22% in the Netherlands [21-22] (Table I). Data on the number of newly diagnosed LCA cases are very limited. The average incidence is estimated to be about 1/75,000 people per year [23].

Detailed data on the epidemiology of IRDs, including those triggered by the *RPE65* gene mutation, are not available in Poland. In their study, Seroczyńska *et al.* [24] found that among individuals under 24 years of age who are members of the Polish Association of the Blind, retinal degeneration was the underlying cause of blindness and significant deterioration of vision in 7.45% of those born between 1999 and 2004 [29]. In a cross-sectional study conducted on a population over 35 years of age (mean age of subjects: 60 years), retinal diseases were observed in 9% of subjects, with RP accounting for 1% of these cases [25].

Based on epidemiological data for European countries, the average prevalence of RP and LCA in the population is about 0.02% and 0.002%, respectively. It can be assumed that the current number of patients with RP and LCA in Poland is approximately 7,700 and 770, respectively. Based on the average prevalence of the *RPE65* mutation in patients with RP and LCA reported in European sources (Table I), there may be a total of approximately 140 patients with this mutation living in Poland.

THERAPEUTIC OPTIONS

The therapeutic management of IRD relies primarily on symptomatic treatment, monitoring of patient condition, education, and rehabilitation. To slow down the progression of retinal degeneration, patients are advised to ensure appropriate photoprotection and use dark tinted spectacles and yellow and orange filters which additionally improve contrast vision. With the aim of improving visual acuity, patients use individually optimized low-vision aids including magnifying glasses and magnifiers. Individuals with very severe visual impairment may rely on electronic devices providing high image magnification capacity. In inherited retinal disorders, genetic counseling and patient education are the only prophylactic methods available [3, 26].

Advancements in molecular biology techniques have contributed to the identification of mutations underlying the development of the disease, which represent potential therapeutic targets in this group of patients. In late 2018, the European Medicines Agency approved the first gene therapy indicated for patients with IRD caused by bialle-

lic mutation of the *RPE65* gene. The goal of treatment is to halt the progression of the disease by delivering a healthy version of the *RPE65* gene to the retinal pigment epithelial cells using the viral gene transfer vector voretigene neparvovec. The treatment restores normal visual cycle and inhibits disease progression [27, 28]. Aside from gene therapy, no approved treatment is available for inhibiting the progression of retinal dystrophy in patients with biallelic *RPE65* mutation.

ECONOMIC BURDEN

Based on the pharmacoeconomic typology, costs that can be measured in monetary units are divided into direct medical and non-medical costs, as well as indirect costs which are understood as referring to resources lost due to the disease and its effects [29]. The economic consequences of visual disturbances, including vision loss, arise from direct medical costs associated with diagnosis and treatment or prevention of potential future health effects such as visual impairment and blindness. Direct non-medical costs comprise expenses related to home adaptation to the needs of individuals with visual dysfunction, as well as costs of transport and professional care. Indirect costs (lost productivity) are linked to sickness absence, and reduced or lost work, both among patients with vision loss and their caregivers [30].

Visual disturbances in patients with the *RPE65* gene mutation occur as early as in the first decade of life. The patients constitute a heterogeneous population with varying degrees of visual impairment, from moderate to complete vision loss [8]. Data on the economic burden associated with IRD caused by the *RPE65* gene mutation are very scanty. The present study analyzes data on the economic burden seen from a broader perspective, i.e., IRD regardless of the genetic cause or loss of vision irrespective of etiology.

Direct medical costs

Direct medical costs refer to the actual expenses associated with the diagnosis, treatment and rehabilitation of patients with a given health condition that are incurred by the healthcare system [34]. Based on the American data, the costs of outpatient visits in the population of patients with RP account for approximately 70% of total annual direct medical costs [31]. Outpatient visits among patients with RP are related not only to diagnostic management, selection and adjustment of medical devices for the visually impaired (low-vision aids), and visual rehabilitation, but also to comorbidities including hearing disorders and nervous system conditions such as depression. Other carriers of direct medical costs include hospitalizations (17% of direct medical costs) and medication costs (12%) [36].

Visual disturbances entail costs resulting from the patient's disability, i.e. vision rehabilitation, and the treatment of depression and injuries caused by physical trauma or falls [32]. Based on the findings of an American study [33], progressive vision loss is associated with a 1.5 times greater risk of depression and injury, and a 2.5-3 times higher frequency of emergency care utilization and hospital admissions compared to the population without visual impairment. Direct medical costs not related to ophthalmic treatment may constitute approximately 36% of excess costs in the population of patients affected by various levels of visual dysfunction (from moderate visual impairment to blindness) compared to the non-visually impaired population [38]. Direct medical costs also include expenses associated with the provision of low-vision aids, such as magnifiers, monoculars, therapeutic filters, and white canes. In addition, visually impaired individuals increasingly use magnifier apps on their smartphones. The frequency of using low-vision assistive devices is the highest among patients with moderate visual impairment (approximately 46%) and the lowest among the blind (24%) [34].

Data on resource utilization and hence medical costs associated with IRD in Poland are very limited and cumulative for the general groups of retinal diseases. According to the National Health Fund (NFZ) data, in 2016 Polish patients with visual impairment caused by retinal and vitreous conditions (excluding age-related macular degeneration) were treated predominantly within the system of specialist outpatient healthcare. The number of visits to ophthalmology outpatient clinics reached approximately 800,000, which was almost 30 times higher than the number of hospitalizations due to the same causes [35].

Regarding low-vision assistive devices, public funding currently covers near and distance glasses, magnifiers, monoculars, magnifying glasses, and binocular glasses. In 2019, the cost of reimbursement of these devices reached approximately PLN 23.5 million [36].

Direct non-medical costs

Direct non-medical costs are defined as actual costs incurred by the healthcare sector to support the process of delivery of medical services but are not related to diagnosis, treatment or rehabilitation [34, 37]. Among the visually impaired, direct non-medical costs refer to expenses associated with devices and aids facilitating communication and mobility, home adaptations, professional home-based patient care, and patient transport [38, 39]. This cost group also includes social benefits, such as disability pensions, sickness benefits, and rehabilitation benefits [34].

Formal home-based patient care, when covered by the healthcare sector in a given country, typically represents the largest component of non-medical costs generated in the population with visual disturbances [43, 40]. In France, average annual costs of formal care accounted for 78% and 93% of annual non-medical costs in the blind and visually impaired populations, respectively. At the same time, the spending on mobility and communication aids and specialized computer software accounted for 20% of non-medical costs in the visually impaired population and 5% among the blind [43].

No data were found that would allow for the estimation of resource consumption and direct non-medical costs as-

sociated with IRD (including *RPE65* gene mutation-related IRD), in Poland. The only data available on non-medical direct costs are social benefit expenses incurred due to eye diseases. An analysis of costs from the viewpoint of public finances extends the public payer perspective to include costs incurred by the Social Insurance Institution (ZUS) or the State Fund for Rehabilitation of the Disabled (PFRON) [34]. Overall, in 2018 ZUS spent a total of PLN 693.7 million on social benefits related to the diseases of the eye (ICD-10: H00–H59) [41]. More than 60% of ZUS spending in 2018 was on disability benefits, and 18% related to sickness absence costs.

Indirect costs

Visual disturbances and vision loss are associated with a loss of productivity resulting from short-term sickness absence from work (absenteeism) or long-term cessation of work following retirement due to disability. Indirect costs also include lost productivity among informal caregivers of visually impaired individuals. Indirect costs indicate production losses which reflect the economic burden incurred by the society as a whole [34].

In their study, Chakravarthy *et al.* [42] applied three different methods to estimate lost productivity due to blindness and moderate to severe visual impairment in 28 European Union countries, including Poland. Depending on the estimation method used, the total cost of productivity loss associated with blindness in Europe was approximately EUR 7.8–17.3 billion, based on the most and least conservative assumptions, respectively. At the same time, indirect costs attributed to blindness in Poland have been estimated at EUR 240–510 million per year. The costs of lost productivity in the population of patients with moderate and severe visual disturbances were slightly higher, amounting to approximately EUR 18.0–39.2 billion for 28 European countries combined (between EUR 0.74 and 1.55 billion in Poland). The average indirect cost per one blind or visually impaired person in Europe per year is estimated at between EUR 20.2 and 56.5 thousand [47].

Data on the cost of lost productivity due to IRD caused by the *RPE65* gene mutation in Poland are limited. The available ZUS data relating to sickness absenteeism are cumulative and allow for the estimation of general indirect costs associated with absenteeism associated with visual disturbances. According to ZUS data, other retinal disorders (ICD-10 H35), visual disturbances (H53) as well as blindness and low vision (H54) caused a total of 34.8 thousand days of sickness absence in adults and 6 thousand days of absence due to childcare [43, 44]. The sickness absence of adult patients and caregivers resulted in indirect costs of PLN 52.5 million and 2.5 million, respectively [34, 42, 45]. The dominant item in the structure of indirect costs was the cost resulting from the patients' own illness due to other retinal disorders (77%), and in the case of children's caregivers – due to visual impairment (81%).

According to ZUS data, a total of 1,900 certificates of incapacity for work were issued in 2019 to patients diagnosed with conditions discussed in the present study, of which 15% were related to first-time disability pensions. A significant proportion of certificates of temporary incapacity for work were issued for a period exceeding 12 months, including 76% first-time certificates and 93% subsequent certificates [46]. Thus, visual disturbances and blindness cause predominantly long-term or permanent incapacity for work. A person who has retired due to disability generates indirect costs until the end of the productive period or until a new employee is found in their place [34].

Costs of informal care

Blind or visually impaired individuals, regardless of the etiology of their disease, require varying degrees of care and support from others. Most often, the caregivers of such patients are individuals in their immediate environment [47, 48]. Providing care to ill/disabled individuals represents a cost from the caregiver's perspective because the time they dedicate to care could be otherwise spent working. Consequently, caregivers generate indirect costs understood as lost productivity [34, 42]. According to a Portuguese study, approximately 40% of patients with visual disturbances receive informal care, and those with poorer visual acuity are more likely to require a caregiver. The average number of hours spent on informal care per year is 470, which translates into an average annual cost of EUR 3.1 thousand per one blind person [49]. In Ireland, the average cost of informal care provided to a blind person has been estimated at approximately EUR 11.7 thousand per year, and it was 2.6 times higher compared to the lost productivity of a single blind person per year [50].

Total costs

The only identified study estimating the economic burden attributable to vision loss in patients with the *RPE65* mutation is the analysis carried out by Viriato *et al.* based on the UK data [37]. The total lifetime cost of vision loss due to the *RPE65* mutation per patient has been estimated at GBP 1.6 million and GBP 1.8 million, assuming the onset of vision loss at the age of 3 or 18, respectively. The authors of the analysis note that the actual cost may be higher, as it is not possible to estimate all categories of both medical and non-medical costs. The combined costs of education, benefits, and other types of publicly funded assistance account for approximately 50% of total annual costs per blind person aged <18 years. Assuming that the onset of vision loss occurs at the age of 18, approximately 70% of the patient's lifetime costs are indirect costs due to lost productivity of the patient and caregivers, while 20% are direct medical costs (figure 3) [37].

The observed high proportion of indirect costs in total costs arises from the fact that individuals with the *RPE65* mutation have a significantly limited ability to undertake work and need to be cared for by others.

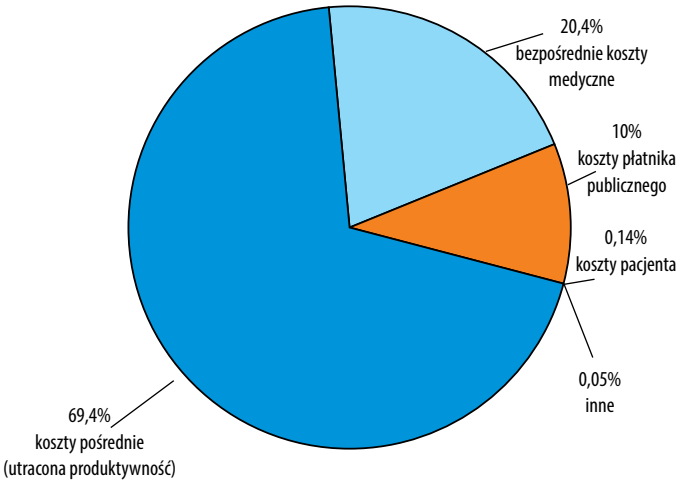

Figure 3. Structure of lifetime costs associated with inherited retinal dystrophy caused by the *RPE65* mutation per patient who lost vision at the age of 18 [37]

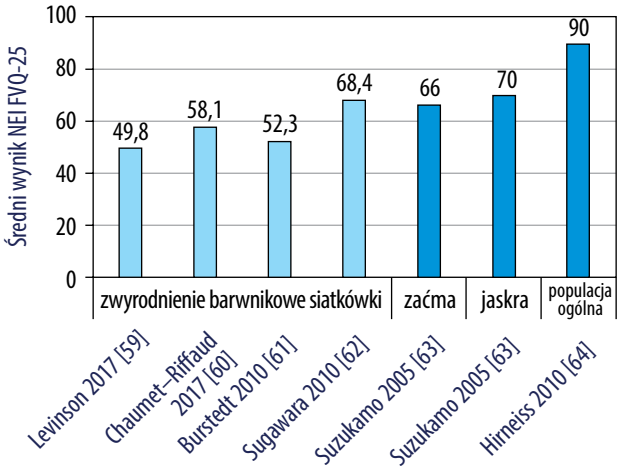

Figure 4. Mean NEI VFQ-25 scores in the population with retinitis pigmentosa, cataract, glaucoma, and in the general population

IMPACT ON QUALITY OF LIFE (UNQUANTIFIABLE COSTS)

Data on the quality of life in patients with IRD caused by the *RPE65* mutation are limited. For this reason, the analysis involved the data of patients with inherited retinal degenerations regardless of the type of causative mutation, and blind people who lost their vision for any reason. The rationale for this approach is that most patients with the *RPE65* gene mutation lose their vision in early adolescence.

One of the instruments used to measure quality of life in patients with visual impairment is the National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The NEI VFQ-25 consists of 25 questions evaluating a range of aspects including general health, vision, social functioning, mental health, difficulties in performing normal activities, and independence [51, 52]. NEI VFQ-25 questionnaire scores range from 0 to 100 (representing the highest quality of life) [53]. In patients with RP, the average NEI VFQ-25 score is 50–68 [54, 55, 56, 57] – similarly to patients with cataract (score of 66) or glaucoma (score of 68.9) [58, 59] (figure 4). A statistically significant deterioration in quality of life as measured by the NEI VFQ-25 questionnaire in patients with RP has been found to correlate with the residual visual field of < 20 degrees and logMAR visual acuity of < 0.3 [60].

Retinitis pigmentosa has a significant adverse effect on the performance of activities of daily living which are dependent on peripheral vision, such as driving at night, walking in low light conditions, identifying faces from a greater distance, and seeing objects outside the central visual field [61]. The most challenging tasks for patients with IRD are related to moving around in dim or excessively bright light, both indoors and outdoors, and steering clear of obstacles outside the central visual field [62].

Visual disturbances have a major impact on patients' mental health. Research findings show that visual dysfunction is a cause of depression and anxiety. In a French study, anxiety was observed in 37% and depression in 16% of subjects in the RP population, compared to 9% and 2% in the non-RP population, respectively [60]. The percentage of patients with RP suffering from depression may be even higher, reaching up to 26% [63, 64].

Patients with visual dysfunction, including IRD, are known to experience limitations in performing the activities of daily living (ADL). Compared to people with normal vision, those with blindness are between 3 and 11 times more likely to require assistance from others in such activities as shopping, eating, and getting around [65]. In an American study, the average time spent by family members caring for a blind person has been found to be approximately 4.3 hours per day. Caregivers responsible for the close monitoring of blind persons for over 2.5 hours per day have been found to face a three-fold increased risk of depression [66].

Polish data on the quality of life of patients with IRD are sparse. A study conducted in Lower Silesia aimed to assess the overall quality of life of people with visual disturbances [67] on the basis of qualitative methods, group interviews, and questionnaires. The study involved patients with varying degrees of visual impairment ranging from correctable visual defects to complete blindness. Of those surveyed, 40% were concerned about their vision because of disease progression, non-acceptance of their condition, high level of inconvenience, and lack of prospects for an improvement in vision [72].

CONCLUSIONS

Inherited retinal degeneration caused by a mutation in the *RPE65* gene is a severe, progressive disease leading to near total blindness as early as in the preschool age or by the second to third decades of life. The data presented above suggest with a high degree of probability that an early onset of disease symptoms and rapid progression leading to vision loss result in a negative impact on the well-being and social and occupational functioning of individuals with the *RPE65* mutation throughout their future life.

Polish reports on the economic burden associated with IRD caused by the *RPE65* gene mutation are scanty. NFZ and ZUS data show that patients with IRD generate direct medical and non-medical costs, including expenses associated with social benefits. Similarly to other countries, short-term absenteeism and patients' premature exit from the labor market lead to reduced productivity and labor supply. Ultimately, this translates into a decrease in generated GDP and impaired GDP growth rate. Based on the World Health Organization (WHO) estimates, vision loss due to causes other than glaucoma, cataract, refractive errors, and age-related macular degeneration accounted for a total of 37,100 disability-adjusted life years (DALYs) lost in Poland in 2016 [68].

As shown by multiple analyses, a large proportion of costs is associated with the incapacity for work and the dependence of visually impaired people on other people. In IRD caused by the *RPE65* mutation, lost productivity among patients and their caregivers is the major component of total costs. Therefore, it is crucial to implement strategies to help the blind and visually impaired to stay in the labor market. To achieve this goal, it is necessary to ensure access to technologies potentially reducing the number of cases of blindness and visual disturbances, which will contribute to decreasing the burden on the health and social care systems, and help improve the quality of life of patients.

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