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PRIMARY TAPETORETINAL DYSTROPHIES AS THE CAUSE OF BLINDNESS AND IMPAIRED VISION IN THE REPUBLIC OF CROATIA

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SUMMARY – According to records of the Croatian Association of the Blind and Impaired Vision Persons, 5,360 blind and impaired vision persons were registered in 2001, with an incidence of 1.3‰. The records contain familial and personal data, data on the underlying disease and ophthalmologic examination findings, including visual acuity of both eyes, fundus examination, biomicroscopic examination and field of vision according to Goldman. Adaptometry, electroretinogram and color perception were rarely performed. Patients were classified according to residual visual acuity, which was converted into percentage of residual vision. During the study, tapetoretinal dystrophies were detected in 328 (6.11%) subjects, 177 (53.9%) male and 151 (46.1%) female. In the Republic of Croatia, tapetoretinal dystrophies as the cause of blindness and impaired vision were recorded in 0.007% (1:14,285) of cases. Over the last 30 years, the number of registered blind and impaired vision persons with this disease increased by 4.3% in large cities in Croatia, whereas its distribution in other areas remained uniform. Clinical manifestations of the disease occurred under the age of 40 in 84.4%, under the age of 50 in 95.2%, and after birth or under the age of 10 in 11.6% of subjects, pointing to the malignancy of the gene for dystrophy of retina pigmentosa. Of all blind subjects, 15.3% belonged to this group. During the study, 40 heredograms were completed, which confirmed the disease to be inherited as an autosomal recessive trait in 40% and autosomal dominant trait in 22.5%, whereas a fresh mutation was probably involved in 37.0% of cases.

Key words: *Blindness, impaired vision, retinitis pigmentosa*

Introduction

Inherited diseases continue to take a leading role today as causes of blindness and impaired vision in the Republic of Croatia[1]. These diseases primarily include tapetoretinal degeneration with a prevalence of 6.11% and accounting for 5.48% of blind persons and those with impaired vision with dystrophy of retina pigmentosa. Tapetoretinal dystrophies are hereditary eye diseases, the most common of them being dystrophy of retina pigmentosa. They are inherited as autosomal recessive, autosomal dominant, or X-chromosome linked (X-linked or sex linked) traits, or may occasionally occur as the result of fresh mutation[2-4]. There are several classifications of tapetoretinal dystrophies. Franceschetti *et al.*[5] have proposed a classification which has served as a basis for Leber's classification into peripheral, macular and diffuse types. Francois considers that these changes should be divided into primary (as listed above) and secondary ones, the latter resulting from hereditary metabolic disturbances[6]. He has proposed a classification according to the type of heredity. The most common tapetoretinal dystrophy is dystrophy of retina pigmentosa, also known as retinitis pigmentosa, primary pigment degeneration of the retina, primary tapetoretinal dystrophy, and dystrophy of the rod and cone. Although this eye disease is very rare, it is wide-

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spread all over the world. The oldest known observation of familial hemeralopia, which may have been related to pigment dystrophy of the retina, was reported by Ovelgun (see ref. no. 5) in 1744. In order to understand the different phenotypical, i.e. clinical presentation, it should be remembered that in case of the recessive mode of inheritance, the disease depends on two pathologic allelic genes. In case of the dominant form, the pathologic gene is more or less supplemented with one normal allelic gene, which explains the large number of different clinical manifestations of retinopathy pigmentosa (interfamilial and intrafamilial). The following diagnostic methods are used to detect changes on the retina: determination of visual acuity with obligatory skiascopy in children, biomicroscopy, ophthalmoscopic fundus examination, and detection of typical changes of retinopathy pigmentosa, adaptometry, determination of visual field and color perception. It is also necessary to perform fluorescein angioretinography, electroretinogram as well as heredogram and audiography. In case of the syndrome, the analysis includes a number of other specialist examinations. Three well known symptoms are characteristic of marked dystrophy of the pigment of retina: narrowed retinal blood vessels, especially arteries; pigment accumulation in the form of so-called bone cells; and waxy pallor of the optic nerve papilla[7]. One of the first functional disturbances in the dystrophy of retina pigmentosa is primary degeneration of the ocular perceptive epithelium, particularly rods. In contrast to primary tapetoretinal dystrophies in which the disease is restricted to the eyes, secondary tapetoretinal dystrophies include diseases in which pigment dystrophy is associated with diseases of one or more organs[8]. They are rarer, although the list of these diseases is quite long, and the presence or absence of retinal pigment degeneration varies depending on the pathologic mechanism and duration of the disease involved.

The aims of the study were as follows: 1) to determine the role of tapetoretinal dystrophies as the cause of blindness and impaired vision in the Republic of Croatia; 2) to confirm territorial distribution of tapetoretinal dystrophies in Croatia; and 3) to study the mechanism of their inheritance.

Subjects and Methods

Data used in the study were obtained from the records of the blind and impaired vision persons from all parts of the Republic of Croatia, controlled by the Croatian Association of the Blind and Impaired Vision Persons. Standard records on the blind and impaired vision persons were obtained from all large centers in the Republic of Croatia. According to the definition of the World Health Organization (WHO) from 1986, completely damaged vision is defined as total loss of vision on both eyes or severe loss of vision on both eyes if the vision on the better eye is less than 0.05 (5%). Persons with residual vision of 6% - 10% on the better eye are classified in the group of severely impaired vision, and those with residual vision on the better eye of 0.1 (10%) to 0.3 (30%) in the group of impaired vision. The records of each person with impaired vision yielded abundant data from personal and family history on the possibly associated underlying disease. In a selected group of 40 study subjects, family trees were constructed. These data were used to complete their heredograms covering at least three generations. Ophthalmologic examination included visual acuity of both eyes, converted into percentage of residual vision; fundus examination; biomicroscopic examination; and field of vision. Test of adaptation and color perception, and electroretinogram were used in all these 40 subjects.

Results

In 2001, 5,360 blind and impaired vision persons were registered in the Republic of Croatia, 328 (6.11%) of them with tapetoretinal dystrophies. Distribution of subjects with tapetoretinal dystrophies, and prevalence (expressed as percentage) of tapetoretinal dystrophies as the cause of blindness and impaired vision according to Croatian counties are presented in Table 1.

Out of 328 individuals with tapetoretinal dystrophies, 177 (53.9%) and 151 (46.1%) were male and female, respectively (Table 2). Classification of the subjects according to their residual visual acuity on the better eye and their sex distribution are shown in Table 3. A modification of the WHO classification was used, defining impaired vision as residual vision on the better eye of 11% - 30% (0.1-0.3); severely impaired vision as residual vision on the better eye of 6% - 10%; and blindness as residual visual acuity of up to 0.05 (5%). Table 3 shows the majority of our subjects to belong to the second group with residual vision on the better eye of 6% - 10%, and the least proportion to be in the group with residual vision on the better eye of 11% - 30%. The percentage of practically blind individuals was relatively high (21.9%). Male predominance was observed in all groups of subjects. Table

Table 1. Number of subjects with tapetoretinal dystrophies and incidence of tapetoretinal dystrophies as the cause of blindness and impaired vision according to Croatian counties

County	No. of TD subjects	TD as cause of blindness (%)
Zagreb – city and county	102	11.2
Krapina – Zagorje	5	3.8
Sisak – Moslavina	6	3.0
Karlovac	8	5.2
Varaždin	9	5.7
Koprivnica – Križevci	5	3.9
Bjelovar – Bilogorje	5	4.1
Primorje – Gorski kotar	51	10.7
Lika – Senj	4	3.4
Virovitica – Podravina	7	5.4
Požega – Slavonia	9	7.0
Brod – Posavina	7	5.0
Zadar – Knin	14	6.3
Osijek – Baranya	39	8.6
Šibenik	10	5.3
Vukovar – Srijem	6	4.5
Split – Dalmatia	43	9.6
Istria	25	6.8
Dubrovnik – Neretva	13	6.5
Međimurje	5	6.3
Total	328	100.0

TD=tapetoretinal dystrophies

Table 2. Sex distribution of subjects with tapetoretinal dystrophies

Sex	No. of subjects	%
Male	177	53.9
Female	151	46.1
Total	328	100.0

Table 4. Tapetoretinal dystrophies according to type of inheritance in 40 selected families

Type of inheritance	No. of subjects	%
Autosomal recessive	16	40.0
Autosomal dominant	9	22.5
X-linked	0	0
Probably fresh mutation	15	37.5
Total	40	100.0

three consecutive generations with transmission from father to son. In 15 subjects, they were the only family members affected with the disease (probably a fresh mutation). In the absence of the latter, sex-linked inheritance might have been involved. It should be emphasized that transmission of dystrophy of retina pigmentosa through two consecutive generations is not an absolute sign of dominance, as it may also be caused by marriage of an affected homozygote (recessive form) to a heterozygote.

Table 3. Blindness and impaired vision in subjects with tapetoretinal dystrophies

	Amaurosis and residual vision (% of total number of subjects)					
	<5% (21.9)		6% - 10% (65.5)		11% - 30% (12.6)	
Sex	M	F	M	F	M	F
n (%)	39 (54.1)	33 (49.9)	114 (53.0)	101 (47.0)	24 (58.5)	17 (41.5)
Total, N (%)	72 (21.9)	215 (65.5)	41 (12.6)			

4 shows modes of inheritance of tapetoretinal dystrophies in the 40 selected subjects, indicating that the autosomal recessive mode of inheritance was most common. All 16 subjects with the autosomal recessive mode of inheritance descended from healthy parents. In all these families there was a brother or sister with dystrophy of retina pigmentosa, or occasionally several brothers or sisters, apart from the proband. In the nine subjects with the autosomal dominant type of inheritance, the disease occurred across

According to the subjects' records, X-linked inheritance of primary tapetoretinal dystrophies was not confirmed.

Discussion and Conclusion

A number of comprehensive studies have been published in the world literature on the issue of retinitis

pigmentosa[9]. Our results are consistent with those reported by others[10,11], who found the dystrophy of retina pigmentosa to be most commonly inherited as an autosomal recessive trait. The male to female ratio is also similar to that recorded in our study for the Republic of Croatia. On the other hand, almost 16% of these cases are inherited as an autosomal recessive trait and 22% as autosomal dominant trait, whereas 9% show an X-linked mode of inheritance. Approximately 50% of the retina pigmentosa dystrophy cases have no familial history and have been called simplex retinopathy pigmentosa[12].

The higher prevalence of tapetoretinal dystrophies in large Croatian cities such as Zagreb, Rijeka, Split and Osijek, could be explained by the fact that many families have moved there from other regions of Croatia because of the higher availability of educational facilities and employment for the blind and impaired vision persons. In the last ten years, the prevalence of tapetoretinal dystrophies in Croatia has changed due to the war and war induced population migration to large cities. Compared with the year 1967, the prevalence of tapetoretinal dystrophies as the cause of blindness and impaired vision increased in large cities by 4.3% on an average (in 1967, tapetoretinal dystrophies were recorded in 5.25%, 6.0%, 7.1% and 4.3% of registered patients in Zagreb, Rijeka, Split and Osijek, respectively). In other areas of the Republic of Croatia, the distribution of patients with tapetoretinal dystrophies is generally uniform. According to the 2001 census, 0.007% (1:14,285) of the population suffered from tapetoretinal dystropheis.

In Croatia, tapetoretinal dystrophy as the cause of blindness and impaired vision is the first (6.11%) among inherited diseases that cause blindness and impaired vision, with dystrophy of retina pigmentosa accounting for 5.48% of cases. Total amaurosis developed by the age of 40 in 17%, residual vision of 5% - 10% by the age of 40 was recorded in 49%, and residual vision of 11% - 30% in 13.0% of subjects. The rate of 15.3% of blind subjects in the 0- to 10-year age group points to malignancy of the gene for tapetoretinal dystrophy. These subjects may come from relatively isolated areas of Croatia, although records of the Croatian Association of the Blind and Impaired Vision Persons contain no data on the origin of the subjects and their families, while classic consanguinity of parents is excluded. Some genetic researches show that the areas of Delnice and Gorski kotar, and of Jastrebarsko are characterized by a higher occurrence of tapetoretinal dystrophies. In these areas, autosomal dominant dystrophies occur, with an early development of cataract and relatively good central vision as compared with the recessive type or fresh mutation, where central vision is destroyed. In some small and relatively isolated areas of Croatia, marriage has only been possible between members of small social communities, thus enabling, through many generations, the encounter of a heterozygote, carrier of the pathologic gene from the potential mutual ancestor. Passing through generations and meeting its allelomorphs, the pathologic gene has most probably intensified its penetrability and expressiveness, and thus by anticipation complemented the heterogeneity and intensity of the clinical presentation of the disease. Consequently, at the moment of birth, the abiotrophic process has advanced, and the children are born blind or have residual visual acuity of up to 10%.

Inherited diseases are still the leading cause of blindness and impaired vision in Croatia. However, as the age of the population has risen, as it has in other European countries and all over the world, the most common causes of blindness are now degenerative diseases, senile maculopathy, vascular diseases of the retina and diabetic retinopathy[13].

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Sažetak

PRIMARNE TAPETORETINSKE DISTROFIJE KAO UZROK SLJEPOĆE I SLABOVIDNOSTI U REPUBLICI HRVATSKOJ

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Prema registarskim podacima Saveza slijepih i slabovidnih u Republici Hrvatskoj 2001. godine bilo je registrirano 5.360 slijepih i slabovidnih osoba uz incidenciju od 1,3‰. Registarski kartoni sadrže obiteljske i osobne anamnestičke podatke vezane za osnovnu bolest i nalaze oftalmološkog pregleda koji obuhvaća vidnu oštrinu oba oka, pregled očne pozadine, pregled procjepnom svjetiljkom te vidnog polja po Goldmanu. Ispitivanje adaptacije, elektroretinogram te ispitivanje osjeta za boje rjeđe su se izvodili. Bolesnici su razvrstavani prema ostatku vidne oštrine koja se preračunala u postotak ostatka vida. U okviru ovoga istraživanja pronađeno je 328 ili 6,11% osoba s tapetoretinskim distrofijama. Od toga je bilo 177 (53,9%) osoba muškog spola i 151 (46,1%) osoba ženskog spola. Učestalost tapetoretinske distrofije kao uzroka sljepoće i slabovidnosti u Republici Hrvatskoj iznosila je 0,007% (1:14.285). U zadnja tri desetljeća veći centri u Hrvatskoj bilježe porast registriranih slijepih i slabovidnih od ove bolesti za 4,3%, dok je u ostalim krajevima Hrvatske rasprostranjenost ravnomjerna. Bolest se klinički manifestirala do 40. godine života u 84,4%, do 50. godine života u 95,2%, a rano nakon rođenja ili do 10. godine života u 11,6% ispitanika, što ukazuje na malignitet gena za distrofiju mrežnice, pigmentozu. U ovoj se dobnoj skupini nalazi 15,3% svih ispitanika koji su slijepi. U ovom je istraživanju izrađeno 40 heredograma na temelju kojih je utvrđeno da se bolest autosomno recesivno nasljeđuje u 40% i autosomno dominantno u 22,5% slučajeva, dok se u 37,0% slučajeva najvjerojatnije radilo o svježoj mutaciji.

Ključne riječi: *Sljepoća, slabovidnost, retinitis pigmentosa*