Clinical study and pattern of inheritance in patients with retinitis pigmentosa

Estudo clínico e padrão de herança em pacientes com retinose pigmentar

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ABSTRACT

***Objective**: To make an epidemiological analysis of patients with retinitis pigmentosa (RP), characterizing clinical aspects of the disease and the pattern of inheritance found in the population studied, according to the presence or not of Usher Syndrome.* ***Methods**: 155 patients with RP were studied and the sample was divided into two groups: group 1 (n = 130) with patients diagnosed with classical RP not associated with systemic symptoms; and group 2 (n = 25) with patients diagnosed with Usher syndrome (USH). We characterized clinical aspects of the disease (sex, age, ocular symptoms, visual acuity and anterior and posterior segment changes) and the pattern of inheritance. Data were obtained through medical history, complete ophthalmic examination and complementary exams (manual visual field, electroretinogram, retinography and fluorescent angiography) for the period of February 2003 to December 2009. We used SPSS version 13.0 for statistical data analysis.* ***Results**: The autosomal recessive inheritance was the most commonly found (76.2% in group 1), but in greater proportion than that of other studies. A smaller number of cases with X-linked recessive pattern (1.5%) was also noted in group 1. There was no statistically significant difference between the clinical characteristics of the two groups.* ***Conclusion**: The pattern of inheritance found in patients with classical RP was similar to that found in other studies. Clinical characteristics were similar in both groups.*

***Keywords:** Retinitis pigmentosa/genetics; Usher syndromes; Inheritance patterns; Genes*

RESUMO

Objetivo: Realizar análise epidemiológica de pacientes com retinose pigmentar (RP), caracterizando aspectos clínicos da doença e o padrão de herança encontrado em nosso meio, de acordo com a presença ou não de síndrome de Usher. **Métodos**: Foram estudados 155 pacientes com RP, tendo sido a amostra dividida em 2 grupos: grupo 1 (n=130), com pacientes diagnosticados com RP clássica, sem associação com alterações sistêmicas; e grupo 2 (n=25), com pacientes diagnosticados com Síndrome de Usher (USH). Foram caracterizados aspectos clínicos da doença (sexo, idade, sintomas oculares, acuidade visual, alterações do segmento anterior e posterior e alterações em exames complementares) e o padrão de herança encontrado. Os dados foram obtidos através de anamnese, exame oftalmológico completo e exames subsidiários (campo visual manual, eletrorretinograma, retinografia simples e fluorescente), no período de fevereiro de 2003 a dezembro de 2009. Foi utilizado o programa SPSS versão 13.0 para análise dos dados estatísticos. **Resultados**: A herança autossômica recessiva foi a forma mais comumente encontrada (76,2% no grupo 1), mas em proporção maior do que a de outros trabalhos da literatura. Um menor número de casos com padrão recessivo ligado ao X (1,5%) também foi notado no grupo 1. Não houve diferença estatisticamente significante entre as características clínicas entre os dois grupos.**Conclusão**: O padrão de herança encontrado nos pacientes com RP clássica foi similar ao encontrado em outros trabalhos. As características clínicas foram semelhantes nos dois grupos estudados.

Descritores: Retinite pigmentosa/genética; Síndromes de Usher; Padrões de herança; Genes

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The authors declare no conflicts of interest

Received for publication: 18/1/2012 - Accepted for publication: 25/7/2012

Introduction

Retinitis pigmentosa (RP) is the most common of inherited retinal dystrophies, with a prevalence of around 1:4000 individuals[1]. RP is subdivided into several types caused by different genetic mutations in different chromosomes and is transmitted by Mendelian and non-Mendelian inheritance. The most common syndrome associated with RP is Usher syndrome (USH), which is transmitted as an autosomal recessive disorder and is characterised by congenital sensorineural hearing loss and vestibular dysfunction. Its prevalence is around 1:100,000[2]. To date there is no effective treatment for RP. Therapeutic approaches involving gene therapy have recently been tested in humans[3,4]. Genetic research will make it possible to classify retinal dystrophies and to provide specific treatment for each type. This study aims to assess differences in the patterns of inheritance among patients with RP and the clinical aspects of the disease with and without Usher syndrome. This paper also aims to inform future studies, especially with regard to the genetics of RP. This is a first step in the study of the correlation between phenotype and genotype.

Methods

A sample of 155 patients with RP seen at the Clinic of Retinal Dystrophies of São Geraldo Hospital, Belo Horizonte (MG), Brazil, was divided into 2 groups: Group 1 (n = 130) included patients diagnosed with classic RP, without systemic involvement, and group 2 (n = 25) included patients diagnosed with USH. The clinical aspects of the disease (age, sex, ocular symptoms, visual acuity, changes in the anterior and posterior segments and changes in diagnostic tests) and the pattern of inheritance were assessed. Data were obtained through medical history, complete ophthalmic examination and diagnostic tests (manual perimetry, electroretinography, simple and fluorescent retinography). The patients were seen at our service from February 2003 to December 2009. A detailed family history, a history of consanguinity and a genogram were obtained to determine the pattern of inheritance for each patient. Statistical analysis was performed using SPSS version 13.0. All analyses used valid percent data, excluding data not obtained through medical history.

Results

There was a predominance of females (55%) in group 1 and males (52%) in group 2. Sixty-five patients with RP (51%) and 18 patients with USH (72%) had a visual deficit for over ten years. The mean age in group 1 was 42.63 years, ranging from 8 to 80 years. The mean age in group 2 was 40.72 years, ranging from 15 to 76 years. Seventy-seven patients (70%) in group 1 and 16 patients (76.2%) in group 2 reported nyctalopia (night blindness), a typical symptom of the disease.

Visual acuity (VA) was measured using best correction on Snellen chart. The classification of legal blindness (VA in both eyes less than or equal to 20/200) and low vision (VA less than or equal to 20/60) took into account the patient's VA only. Fifty-seven patients (43.9%) in group 1 and 6 patients (25%) in group 2 were legally blind. Twenty-four patients (18.5%) in group 1 and 2 patients (8%) in group 2 had a VA higher than 20/60 in both eyes.

On biomicroscopy of the anterior segment, most patients in group 1 (52.1%) had no alterations and 28 patients (23.5%) had cataract in at least one eye. In group 2, ten patients (41.7%) had cataract.

Assessment of the posterior segment showed fundus changes typical of the disease: A pale optic disc, vascular attenuation and bone-spicule pigmentation. The severity of these findings can be highly variable, and the disease may present without the full triad. Vitreous changes were also frequently seen, mainly mild opacities associated or not with vitreous detachment. Mild opacities only, not associated with posterior vitreous detachment, were seen in 52.7% of patients in group 1 and 60% of patients in group 2.

Both manual perimetry and electroretinography (ERG) showed severe changes in both groups (Table 1). Severe changes were defined as losses in central vision with results lower than 20º on perimetry and an absence of recordable responses on ERG.

The most common pattern of inheritance was autosomal recessive, seen in 99 patients (76.2%) in group 1 and 14 patients (58.3%) in group 2 (Table 2).

Discussion

Although most cases of RP have a monogenic aetiology, considerable genetic heterogeneity exists. Mendelian patterns of inheritance involved in RP have been frequently studied, being traditionally divided into autosomal recessive, autosomal dominant and X-linked recessive[5,6]. In addition, other types of inheritance have been associated with RP, such as mitochondrial and digenic inheritance. Isolated cases are those in which the

Table 1

Proportion of severe changes found on manual perimetry and electroretinography (ERG) in groups 1 and 2

Severe changes	Group 1 Classic RP (%)	Group 2 Usher Syndrome(%)
Manual Perimetry (central visual lower than 20º)	67,4	83,3
ERG (absence of recordable responses)	70	80

Table 2

Patterns of inheritance found in groups 1 and 2

Pattern of inheritance	Group 1 Classic RP (%)	Group 2 Usher Syndrome(%)
Autosomal recessive	76,2	58,3
Autosomal dominant	18,5	-
X-linked autosomal recessive	1,5	-
Isolated cases	-	41,7
Indeterminate	3,8	—
Total	100	100

family history is entirely negative. These, however, may in fact be caused by new mutations, autosomal recessive inheritance or patterns of inheritance only detectable through genetic analysis at the molecular level. More than 45 genes have already been linked to RP and several studies have been conducted to establish its phenotypic expression[7-9]. Most cases of autosomal dominant RP are caused by mutations in the rhodopsin gene[10]. Among the main genes responsible for autosomal recessive inheritance are those producing proteins of the phototransduction cascade in rods, such as phosphodiesterase or ion channel proteins, as well as CNGB1, ABCA4 and RPE65. The RPGR gene is responsible for over 70% of cases of sex-linked recessive inheritance[11,12].

USH is classified into three types: Type 1 (USH1) shows profound congenital deafness, absent vestibular function and progressive RP; Type 2 (USH2) shows moderate to severe congenital deafness, normal vestibular response and progressive RP with onset in adolescence, corresponding to about half of the cases; and Type 3 (USH3) is characterised by progressive hearing loss, variable vestibular response and RP with onset in adolescence. The first identified gene was the USH1 gene, MYO7A, which belongs to a class called the myosin superfamily. Other genes have been identified for other types USH, with various mutations[2].

In our study, classification of the pattern of inheritance was done using the genogram obtained on medical history, with the largest possible number of generations. Detailed information about family history of eye disease and consanguinity was also obtained. In group 1, the most common pattern of inheritance was autosomal recessive, in which isolated cases were included, followed by autosomal dominant and X-linked recessive. In group 2, all cases were autosomal recessive. The pattern of inheritance was considered as indeterminate in unclear cases where it was not possible to establish a specific family pattern. A molecular genetic study will be the next step for assessing the correlation between phenotype and genotype in RP. True correlations are known to exist between specific types of mutations and phenotypic presentations.

The clinical features of the disease in the two groups, such as VA, the presence of cataract and vitreous changes, were assessed. Severe changes in perimetry and ERG were seen in a large proportion of patients, with a high degree of functional impairment.

No statistically significant differences on the chi-square test were seen between the clinical features of groups 1 and 2.

Conclusion

Worldwide RP studies have classified the predominant types of inheritance in each region. In our study, we determined the proportions of different patterns of inheritance in the sample and their correlation with previous studies in Brazil and abroad. Autosomal recessive inheritance was the most common pattern, in agreement with the literature. In our study, this pattern of inheritance was more frequent than in other Brazilian and worldwide studies. Also, fewer cases of X-linked recessive inheritance were seen. These differences may be due to epidemiological variability or to the smaller number of patients in our sample. The frequency of dominant and indeterminate inheritance was similar to previous studies.

Determining the patterns of inheritance involved in RP is critical to enable future molecular genetic studies and to assist in the creation of a national database.

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