USHER'S AND HALLGREN'S SYNDROMES

S. MERIN, F. A. ABRAHAM, E. AUERBACH

Department of Ophthalmology and the Vision Research Laboratory, Hadassah University Hospital, Jerusalem, Israel

A study has been made of 35 patients belonging to 20 families, all diagnosed as Usher's syndrome (retinitis pigmentosa and deafness). The results indicate that there are four clinical types, which have been called Types I to IV. Genetically, they represent at least two, and possibly three or four, separate entities.

The association of retinitis pigmentosa with deafness was first reported by von Graefe more than a hundred years ago (von Graefe 1858), but it was the British ophthalmologist, Usher (1914), who stressed its hereditary nature. He showed that 11 out of his 69 patients with retinitis pigmentosa were deaf, and that in the same families all patients were similarly affected. Later several investigators (Lindenov 1945, Hallgren 1959, Amman et al. 1965) showed independently that this is not a fortuitous combination, but a true genetic syndrome.

Usher's syndrome is not rare. About 10% of all patients with retinitis pigmentosa are deaf (Bell 1933). Statistical-genetic studies in various countries have established the prevalence of the syndrome to be between 1.8 and 3.5 cases per 100,000 (Table 1).

TABLE 1

PREVALENCE OF THE USHER-HALLGREN SYNDROMES: STATISTICAL-GENETIC STUDIES

Country	Prevalence (cases per 100,000)	Reference
Denmark	3.0	Lindenov 1945
Sweden	3.0	Hallgren 1959
Switzerland	1.8	Amman et al. 1965
Finland	3.5	Nuutila 1970

A few words on nomenclature are important. Usher's syndrome is the name most commonly used to define the specific association of deafness with retinitis pigmentosa (Vernon 1969). However, the term Hallgren's syndrome is also used as a means of identifying the syndrome with the author of the most extensive study made to date (Hallgren 1959). In addition, the term Usher-Hallgren syndrome (Forsius et al. 1971) is in common usage. Recently

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the names retinitis pigmentosa-dysacusis (Nuutila 1967, Toivakka and Nuutila 1967) or dystrophia retinae-dysacusis syndrome (Nuutila 1970, Forsius et al. 1971) have been suggested as descriptive terms. We prefer to use the name Usher's syndrome, which is the best known and most unpretentious for the disorder in general, and to limit the use of Hallgren's syndrome to the Type III variant (see below). Should the biochemical background become known in the future, this may all be changed. For the same reason, we shall use the term retinitis pigmentosa which, although it is not the ideal name for the disorder, is the most accepted (at least in the western hemisphere).

The present study is based on clinical, genetic, audiologic, and electroretinographic findings in 35 patients belonging to 20 families who have been seen in the Vision Research Laboratory or in the Genetic Service of the Eye Department of Hadassah Hospital. All had been sent for consultation because of visual disturbances. We have been able to distinguish four clinical types of Usher's syndrome, which represent at least two, and possibly three (or four) distinct genetic types. I would like to describe each of them in order of their frequency.

Usher's Syndrome, Type I

This consists of retinitis pigmentosa, congenital complete deafness, practically no vestibular response to caloric or rotatory excitation (in most cases), and normal mental development without any neurologic deficit. This type was by far the most common, with 21 patients belonging to 12 families being affected.

The retinal changes were typical for retinitis pigmentosa, and were age-related. None of the patients was born blind. The earliest change observed was a greyish tapetal reflex, sometimes resembling a retinitis punctata albescens. Later pigmentary stippling could be seen and still later, pigment in the form of " bone corpuscles " appeared, first in the periphery and afterward in the posterior pole.

Lens changes became more pronounced with age, starting with posterior subcapsular cataracts and progressing to mature cataracts.

Visual acuity varied between 6/6 and 6/12 in the first two decades of life, dropping to between 6/30 and 6/60 or less in the third decade, and to finger counting in the fourth and fifth decade in all of our patients. The visual fields showed changes typical for retinitis pigmentosa, often reaching tubular vision towards the end of the second decade of life. Color vision was usually normal, but sometimes unclassifiable abnormalities, a tendency to tritanopia or to a scotopic line, have been noted.

The electroretinogram (ERG) was in most cases extinct; in others it was extremely small, the positive wave not exceeding 40 microvolts in any case, which is no more than about a tenth of the minimal normal value in our laboratory. Fig. 1 shows that the ERG of our youngest patient was practically extinct at the age of 2½ years. The visual evoked potential (VEP) was subnormal to extinct in all cases examined.

All patients in this group were both deaf and mute. They were all deaf from birth, although the deafness was usually not discovered until the second year of life. The audiograms revealed severe deafness in all cases. Fig. 2 shows a typical audiogram of one of the patients in this group. A rotatory and caloric test for vestibular function was performed in 8 patients, and all but one showed a nonresponsiveness of the vestibulum. All patients had normal mental and motor development; no neurologic deficiencies could be detected.

Fig. 3 shows a pedigree of one of the families with this syndrome. In all cases where one of the members of the family had the Type I syndrome, all others who were affected showed similar clinical signs.

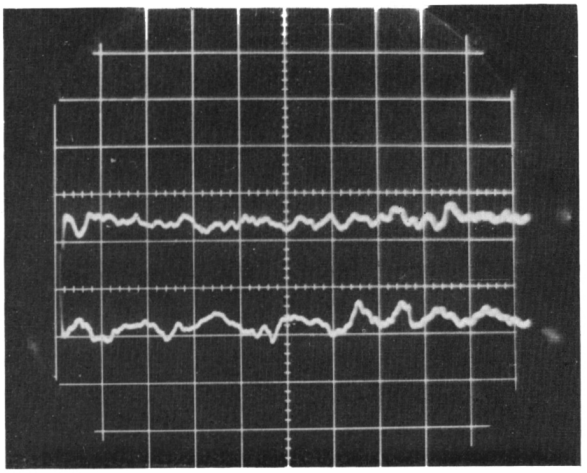

Fig. 1. ERG of a 2½ year old patient with Usher's syndrome, Type I. There is practically no retinal response even at this early age.

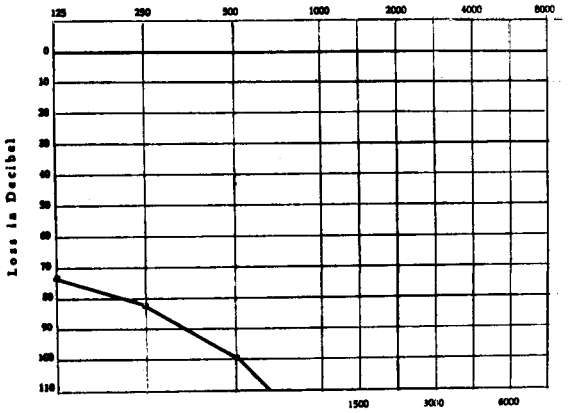

Fig. 2. Audiogram of a patient with Usher's syndrome, Type I.

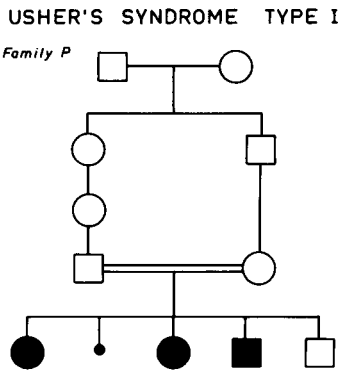

Fig. 3. Pedigree of a family with Usher's syndrome, Type I.

Usher's Syndrome, Type II

This consists of retinitis pigmentosa, a slowly progressive hearing defect, normal vestibular function in most cases and normal mental and neurological findings. Nine patients, belonging to 4 families suffered from this type of Usher's syndrome. Genetically it seems distinctly different from Type I, with different families being affected. In one such family (Fig. 4) all of the affected members had the same signs and symptoms.

The retinal changes seemed to be much milder functionally than in Type I. However,

as in Type I, cataracts were present, and the ERG was practically extinct in all cases. Functional deterioration was more slowly progressive than in Type I.

One patient at 52 years of age still had a visual acuity of 6/9, although his vision was tubular. His sister, 50 years old, had 6/9 vision after cataract extraction. In both, the fundus showed typical pigmentary bone corpuscles.

The VEP was examined in 3 patients, and in 2 of them was found to be remarkably good, probably because of good macular function.

Audiometrically the patients showed a loss of around 60-70 decibels in the higher frequencies, and much less in the lower ones (Fig. 5). Some patients were less affected. Our impression is that they become progressively worse with advancing age. The vestibular function was normal in most cases and there were no abnormal mental or neurologic findings.

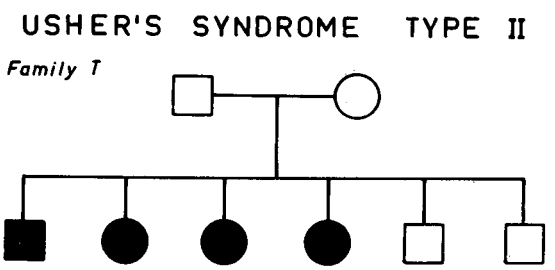

Fig. 4. Pedigree of a family with Usher's syndrome, Type II.

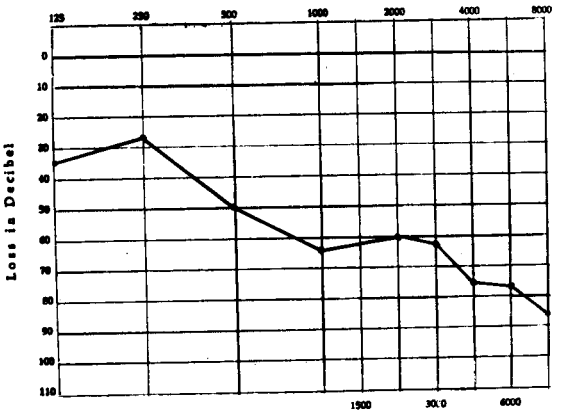

Fig. 5. Audiogram of a patient with Usher's syndrome, Type II.

Usher's Syndrome, Type III

In this type, retinitis pigmentosa is combined with complete congenital deafness, as in Type I, but in addition vestibular ataxia was present. I would like to call this Hallgren's syndrome because 90% of the patients described by Hallgren (1959) in his large Swedish study were of this type.

In our series only 2 patients, each stemming from a different family, had this syndrome (Fig. 6). There was no other affected member in any of the two families, so we cannot be certain that genetically, it is not merely a variant of Type I. Both patients showed a total unresponsiveness of the vestibular apparatus. The vestibular ataxia was mild, presenting itself mainly in a swinging gait and a tendency to fall to one side when walking with closed eyes.

Usher's Syndrome, Type IV

This type consisted of retinitis pigmentosa and congenital deafness, as Type I, but in addition mental retardation was present. It was found in 2 out of 3 affected members in 2 fam-

ilies (Fig. 7). Like Type III, this could be either a genetically distinct type, or just a variant of Type I, the mental retardation being unrelated to the genetic syndrome. Two pedigrees are shown in Fig. 7. The eldest sister in family U was mentally retarded at the age of 24, but the affected 4-year-old younger sister did not seem retarded.

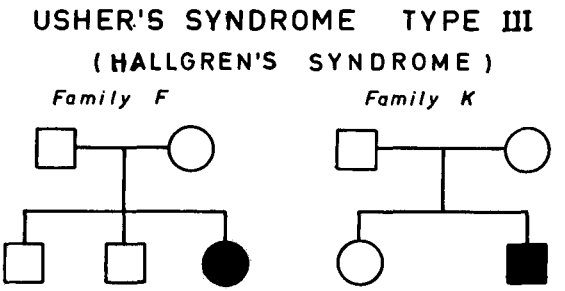

Fig. 6. Pedigrees of two families with Usher's syndrome Type III, (Hallgren's syndrome).

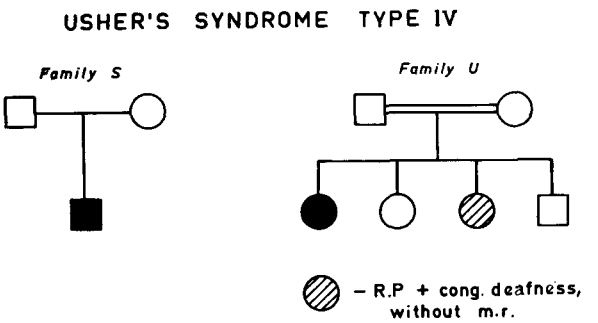

Fig. 7. Pedigrees of two families with Usher's syndrome, Type IV.

Table 2 summarizes our present thoughts on Usher's syndrome, or rather, syndromes. There are four clinical types. Types I and II are caused by two different autosomal recessive genes. Types III and IV could be either separate genetic entities or, alternatively, variants of Type I caused by the same gene with different expressivity.

TABLE 2

PRINCIPAL CLINICAL FINDINGS IN FOUR TYPES OF USHER'S SYNDROME

Type	Retinitis pigmentosa	Complete congenital deafness	Progressive hearing impairment	Vestibular ataxia	Mental retardation
I	+	+			
II	+		+		
III	+	+		+	
IV	+	+			+

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DISCUSSION

There is considerable evidence in the literature supporting the concept of four different syndromes. Hallgren, in his Swedish study, mentions that if one member of a family had a slight hearing defect or a severe one, all other patients in the same family were similarly affected. Also McLeod et al. (1971) stressed that the degree of severity of deafness was similar within a given sibship. De Haas et al. (1970) found that the ocular, audiologic, and vestibular affection tended to be of the same degree in all affected members of one family. Nuutila (1970) concluded from his study that there are two genetically unrelated types of Usher syndrome roughly corresponding to our Types I and II; Nuutila thought that the second type might be nongenetic because all his four cases stemmed from four different families. Our study proves that Type II is a hereditary disease like Type I.

Another indication for considering the different types as being separate genetic entities lies in the reported clinical descriptions of cases of Usher's syndrome. In Sweden (Hallgren 1959) 90% of all patients had vestibular ataxia and almost 25% of all patients were mentally defective, suggesting a high prevalence of Usher's Types III and IV. In Finland (Nuutila 1970) Type II was very rare, occurring in only 4 out of 138 patients with Usher's syndrome. In the large genetic isolate of Usher's syndrome in southwestern Louisiana, all patients seemed to suffer from Usher's syndrome Type I (Kloepfer et al. 1966). On the other hand, Usher's syndrome seems to be very rare in Poland (Kapuscinski et al. 1969).

The two, or four, syndromes of Usher are caused by autosomal recessive genes. There is little indication for the existence of another dominant type of this syndrome, although such a possibility has been mentioned (Montandon et al. 1957). The tapetoretinal degeneration in all cases was of the " retinitis pigmentosa type ", and not of the rare congenital tapetoretinal degeneration (amaurosis congenita of Leber) type. This was also shown in a study on Leber's amaurosis (Karel and Sedlackova 1967).

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S. Merin, M.D., Department of Ophthalmology, Hadassah University Hospital, P.O. Box 499, Jerusalem, Israel.