

Usher syndrome in the city of Birmingham—prevalence and clinical classification

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Abstract

Aims—To estimate the prevalence of Usher syndrome in the city of Birmingham, and to establish a database of patients who have been classified into different clinical subtypes essential for future gene mutation analysis.

Methods—Symptomatic cases of Usher syndrome (US) resident in the city of Birmingham in June 1994 were ascertained through multiple sources. Ophthalmic and audiological reassessment together with examination of medical records and patient questionnaires allowed classification of three subtypes, US 1, US 2, and US 3. In addition, family pedigrees were examined and blood was taken from index patients for DNA extraction.

Results—In the population aged over 15 years the prevalence was 6.2 per 100 000 population for all US subtypes. The prevalence for US 1 and US 2 was 5.3 per 100 000 population. This is greater than previously reported. In the age group 30–49 years the prevalence approached 1 in 10 000. Clinical classification found 33% US 1, 47% US 2, and 20% US 3.

Conclusion—This higher prevalence rate and greater frequency of US 2 and US 3 may reflect a more complete ascertainment.

(*Br J Ophthalmol* 1997;81:46–53)

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Accepted for publication
14 October 1996

The Usher syndromes (US) are a heterogeneous group of autosomal recessive disorders characterised by congenital hearing loss associated with a progressive pigmentary retinopathy. This association was first described by von Graefe,¹ but it was Charles Usher who first emphasised its familial occurrence.²

Three clinical types are recognised which are largely distinguished by differences in hearing and vestibular function and not by ophthalmic criteria (see Table 1).^{3–5}

Patients with US 1 are characterised by profound congenital sensorineural deafness, impaired speech development, and are seldom helped by hearing aids. Another feature is the congenital absence of vestibular function manifest in infancy as a delay in motor development, and in the adult as a non-progressive ataxia. Recent linkage studies have shown that there are three genes responsible for US 1. The first was located to the long arm of chromosome 14 in 10 French families,⁶ with two further loci on the long and short arms of chromosome 11.^{7,8} Most type 1 patients (75%) have a mutation at 11q13.5, and this gene has

now been identified and found to code for an unconventional myosin protein which also causes the Shaker-1 phenotype of mice.^{9,10}

Patients with US 2 demonstrate a congenital non-progressive moderate to severe hearing loss which is milder in the low frequencies. They obtain benefit from hearing aids and have good speech development. Vestibular function is normal.⁵ US 2 has been located to 1q using 30 families from the USA, Sweden, and Italy,^{11,12} but may also show locus heterogeneity.¹³

The phenotype of US 3 has been recently described; normal hearing development but deterioration in the absence of exogenous or other causes occurring between the first and fourth decade, resulting in a moderate to profound hearing loss. Speech development is normal and vestibular function is variable.¹⁴ US 3 is more common in Finland and linkage shows a locus at 3q21–25.¹⁵

Progressive pigmentary retinopathy is usually typical for retinitis pigmentosa in all clinical types, but is often diagnosed earlier in US 1, and it is suggested that the combination of visual and vestibular impairment causes functional impairment earlier,¹⁶ although a similar percentage of patients maintain central visual acuity of 6/60 or better until the fifth or sixth decade.¹⁷

Prevalence of US varies according to the population base screened and ranges from 1.8 to 4.4/100 000 in the general population,^{18–22} 13–20% in the retinitis pigmentosa population,^{19,20,23,24} 1–6% among congenitally deaf individuals,^{22,25,26–29} to as high as 30% in certain deaf population isolates.^{20,30} However, only limited prevalence data are available from the UK.²⁷

The purpose of this study was twofold. Firstly, to estimate the prevalence of Usher syndrome in the city of Birmingham and, secondly, to establish a database of patients who have been accurately categorised into the different clinical subtypes—essential for molecular studies and for genetic counselling among families.

Methods

PREVALENCE

An attempt was made to ascertain through multiple sources all symptomatic patients with Usher syndrome resident in the city of Birmingham on 30 June 1994 which relates to the most recent annual population statistics for the city (see Table 2). A genetic eye clinic and a diagnostic index have been held in Birmingham since 1977.

All ophthalmologists and optometrists who practise in the city were contacted and asked for names of patients with US. Ophthalmologists see patients at one of five hospitals in Birmingham but none of the eye departments carries a diagnostic index. However, retinal function tests are performed at the Visual Function Unit, Birmingham and Midland Eye Hospital (BMEH) with record books dating back to 1986, and this provided a further source of ascertainment.

SENSE (the National Deafblind and Rubella Association) is a national voluntary organisation which holds a database of patients with US in the UK who use this service. SENSE provided names of patients who were not known by us at the time of contact.

Contact was also made with psychiatric services for the profoundly deaf at the Queen Elizabeth Psychiatric Hospital in Birmingham.

Head teachers of schools for the deaf and six secondary schools with deaf units were contacted. There are currently 55 pupils at the only secondary school for the deaf which serves Birmingham and the West Midlands. Since 1990, children attending this school have been routinely screened by one of the authors (ARF). Deaf children are not routinely screened by an ophthalmologist at other schools; therefore ascertainment depended on the presence of visual symptoms. For this reason it was decided to make the lower age limit for the prevalence study 15 years, since some with US 1 do not become symptomatic until the beginning of the second decade and children with US 2 do not become symptomatic until the latter part of the second decade or beginning of the third decade.^{3 17}

Specific otolaryngological and ophthalmological criteria used for accepting patients as having US 1 and 2 were those recommended by Smith *et al*, and which have been adopted by the Usher Syndrome Consortium⁵—that is, US 1: congenital severe to profound sensorineural hearing loss, and absent vestibular function, associated with a pigmentary retinopathy or reduced responses consistent with a retinal dystrophy on ERG testing; US 2: congenital mild to severe sensorineural hearing loss with normal vestibular function associated with a pigmentary retinopathy or reduced responses consistent with a retinal dystrophy on ERG testing. A diagnosis of US 3 was considered when there was later onset of hearing loss which was moderate to profound, reliable evidence of deterioration of hearing impairment with other possible causes of deterioration excluded,¹⁴ and associated with a pigmentary retinopathy or reduced responses consistent with a retinal dystrophy on ERG testing.

Diagnosis of US in index patients was verified by clinical reassessment of cases in an ophthalmic department, or evaluation of medical records (see Tables 4, 5, and 6). Birmingham City was defined by census, and residency on ascertainment day was confirmed with patients and/or with their general practitioners

CLINICAL ASSESSMENT

Patients located through these sources were contacted by mail and invited to participate in the study. A questionnaire was sent to each patient requesting information about the history of their vision and hearing impairment, their general health, and family history of genetic disease. General practitioners were also contacted to request any additional medical information about their patients.

Each patient enrolled in the study was assessed in a standardised manner to verify their clinical diagnosis of US, and for clinical subtyping. The ophthalmic and audiovestibular evaluation was based upon recommendations by the Usher Syndrome Consortium (USC).⁵ A pedigree was taken for each family and a blood sample from affected patients for measurement of phytanic acid levels, and for search of the 3243 mutation of mitochondrial DNA (to exclude rarer causes of retinitis pigmentosa and sensorineural deafness) and for extraction of DNA for gene mutation analysis.

AUDIOVESTIBULAR EVALUATION

The audiovestibular evaluation is summarised below.

Clinical interview

- 1 Age at which hearing loss was first recognised
- 2 Speech development
- 3 History of otological or neurological surgery
- 4 Temporal progression of hearing loss or vestibular function
- 5 History of other audiovestibular symptoms (vertigo, tinnitus, unsteadiness, etc).

Otological/audiological evaluation

- 1 Otoscopy
- 2 Pure tone audiogram and tympanometry.

Vestibular evaluation

- 1 Romberg and Unterberger tests
- 2 Assessment of gait
- 3 Caloric stimulation: 50 ml of water cooled to 20°C used to irrigate each ear for 30 seconds with the patient supine and head flexed to 30 degrees. Vestibular function was considered normal in the presence of nystagmus associated with a sensation of vertigo.

OPHTHALMIC EVALUATION

The ophthalmic evaluation is summarised below.

- 1 History of visual symptoms and diagnosis of pigmentary retinopathy, presence and treatment of cataracts
- 2 Visual acuity (best corrected)
- 3 Goldmann fields
- 4 Slit-lamp evaluation/presence and type of cataract
- 5 Fundus examination
- 6 ERG.

Scotopic corneal ERGs were recorded following 20 minutes of dark adaptation, using a Ganzfeld stimulator with intensities of 2.8 and 18 foot-lamberts (ft-l), (standard flash and 1 log unit greater than standard flash). Photopic

Table 1 Usher syndrome (US) phenotype

| | US 1 | US 2 | US 3 |
|----------------------------------|--|--|--------------------------------------|
| Age at diagnosis of hearing loss | 0–2 years | 0–6 years | During first and up to fourth decade |
| Audiogram | Profound hearing loss/ non-recordable threshold | Moderate to profound high frequency hearing loss. Non-progressive | Progressive hearing loss |
| Cold caloric test | Absent | Nystagmus | Variable |
| Speech | Unintelligible | Intelligible | Intelligible |
| Pigmentary degeneration | Present | Present | Present |
| ERG | Reduced | Reduced | Reduced |

and 30 Hz flicker was obtained using 18 ft-l stimulus and 30 ft-l background illumination. Peak to peak measurements were taken.

Patients with a profoundly reduced ERG or whose Goldmann visual fields were less than 20 degrees maximum diameter at their last assessment did not have these tests repeated.

Patients were diagnosed and typed according to findings shown in (Table 1). Six years was set as the upper age limit for diagnosis of hearing loss in US 2 allowing for the fact that this was largely based on the patients' own historical information.

Patients who did not fit US 1 or 2 were initially classified as atypical. Criteria for the clinical diagnosis of US 3 have been recently described; thus some atypical patients were reclassified as US 3 when previous audiological tests were available for comparison or where anamnestic information supported this diagnosis (Table 1).¹⁴

Results

PREVALENCE STUDY

A total of 31 index patients were identified (Table 2), 18 of whom were ascertained through more than one source. Seventeen of 19 affected siblings ascertained were also resident in the city on ascertainment day, together with three affected relatives outside the index patient's sibship. Two affected siblings were not examined for the prevalence estimate because they were under the age of 15 years.

Table 2 Sources of ascertainment of index patients

| Source | No of patients ascertained* |
|---|-----------------------------|
| Diagnostic index of department of clinical genetics | 24 |
| Practising ophthalmologists | 2 |
| Practising optometrists | 0 |
| Record book of visual function unit at BMEH | 14 |
| Schools for deaf including schools with special units | 3 |
| SENSE (National Deafblind and Rubella Association) | 3 |
| Psychiatric services for the deaf (Queen Elizabeth Hospital Birmingham) | 4 |
| Total index patients | 31 |
| Number of secondary cases | 18† |
| Total probands in prevalence study | 49 |

*18 probands were ascertained more than once.

†The assessed relatives who were living in the city of Birmingham in June 1994 and who were aged over 15 years.

Table 3 Age distribution of patients in mid June 1994

| Age group | No resident | No with US* | Prevalence | Prevalence of all US per 100 000 | Prevalence of US 1 and 2 per 100 000 |
|-----------|-------------|-------------|-------------|----------------------------------|--------------------------------------|
| 15–29 | 233 329 | 12 | 1 in 19 444 | 5.1 | 5.1 |
| 30–49 | 264 351 | 25 (21) | 1 in 10 574 | 9.5 | 7.9 |
| 50–69 | 183 747 | 9 (6) | 1 in 20 416 | 4.9 | 3.3 |
| 70–85+ | 106 719 | 3 | 1 in 35 573 | 2.8 | 2.8 |
| Total | 788 146 | 49 | 1 in 16 085 | 6.2 | 5.3 |

*Numbers in parentheses refer to patients with Usher syndromes 1 and 2 (where this is different from the total).

This gave a total of 49 patients, 22 males and 27 females, with US (age range 16–75 years).

Estimated resident population statistics for mid June 1994 in the age range 15–85+ years totalled 788 146.³¹ This gave a prevalence of 1 per 16 085 or 6.2 per 100 000 population for all US subtypes. In the age range 30–49 years the prevalence was 1 per 10 574. Prevalence of US 1 and US 2 was 5.3 per 100 000 population (Table 3).

CLASSIFICATION OF US SUBTYPES

Twenty three of 31 index patients have been clinically reassessed in an ophthalmic department, and in six families (four US 1, one US 2, and one US 3) one affected sibling was clinically re-evaluated. Of the remaining eight index patients, two declined participation and two failed to respond. Questionnaires were completed by all index patients except those two non-responders. Examination of medical records and questionnaires has allowed clinical classification in all but one index patient where there were insufficient clinical data, giving a total of 30 index patients. An attempt was made to obtain previous audiology reports to verify the non-progressive nature of the hearing loss or to identify a true progression in those patients who considered their hearing loss to have progressed.

Phytanic acid levels were normal in all patients, and none had the 3243 mitochondrial mutation.

The respective proportion of cases were 10 (33%) US 1, 14 (47%) US 2, and six (20%) US 3.

US 1 FAMILIES (TABLE 4)

Ten index patients were classified as US 1. Eight of 10 were clinically reassessed in an ophthalmic department and in two medical records and patient questionnaires were examined.

Hearing loss was diagnosed in infancy, patients had poor speech, and had never gained benefit from hearing aids. Audiometry thresholds were non-recordable in all patients, and in the eight patients who were clinically reassessed vestibular function was absent. Two patients have not had vestibular function testing. Historically five reported delay in walking until 18–24 months of age, with five having no recall. Three recalled poor balance as a child, clumsiness, and inability to ride a bicycle.

Diagnosis of pigmentary retinopathy was made between 8 and 34 years, (mean age 19 years) with onset of symptoms reported between 12 and 24 years (mean age 16 years). Nyctalopia was symptomatic before loss of

Table 4 Patients with Usher syndrome 1—clinical information

| No | Age/sex | Age/diag deafness | Audio gram | Vestibular function | Age diag RP (years) | Age visual symptom (years) | VA better eye | ERG (mV) | Cat | Field (°) | Pigment degen |
|-----|---------|-------------------|------------|---------------------|---------------------|----------------------------|---------------|----------|---------------------|-------------|----------------------------|
| 10* | 47/M | Infant | NR | neg | 21 | 15 | 3/60 | ext | no | 10 | Extensive Atrophic maculae |
| 11* | 45/F | Infant | NR | neg | 22 | 22 | PL | ext | no | <5 | Extensive Atrophic maculae |
| 18* | 23/F | 2 years | NR | neg | 23 | 21 | 6/9 | ext | no | 20 | Extensive |
| 22* | 25/F | Infant | NR | neg | 17 | 12 | 6/12 | ext | no | 10 | Moderate |
| 24* | 46/F | 2 years | NR | neg | 18 | 24 | 6/12 | ext | bilat pseudo phakos | 5 | Extensive Macular pigment |
| 25* | 36/M | Infant | NR | NP | 8 | 13 | 3/60 | ext | no | <5 | Extensive |
| 27 | 34/F | 2 years | NR | NP | 15 | 12 | 6/9 | ext | no | 10 | Extensive |
| 28 | 21/M | Infant | NR | NP | 18 | 15 | 6/9 | <75 | no | constricted | Moderate |
| 32* | 23/M | 2 years | NR | neg | 12 | 12 | 6/6 | ext | no | constricted | Moderate |
| 36* | 39/F | Infant | NR | neg | 34 | 18 | 6/12 | ext | early PSLO | 20 | Extensive |

RP = retinitis pigmentosa; NR = non-recordable; NP = not performed; PSLO = posterior subcapsular lens opacities; ext = extinguished; Cat = cataract; diag = diagnosis; pigment degen = pigmentary degeneration; *clinically reassessed.

peripheral field. In all cases the ERG was extinguished or profoundly reduced, visual fields were constricted, and pigmentary degeneration was typical for retinitis pigmentosa with peripheral bone spicule pigmentation. Poor central vision was attributable to macular pigmentation and atrophy in three cases. One patient (case 24) was pseudophakic with lenses removed at 39 years. With the exception of mild lens opacities seen in case 36, no other patient had lens opacities. Affected siblings of cases 11, 18, 24, and 32 were clinically reassessed and found to be typical for US 1.

US 2 FAMILIES (TABLE 5)

Fourteen index patients were typed as US 2. Eleven of 14 were clinically reassessed in an ophthalmic department and in three medical records were evaluated. Hearing loss was diagnosed by the age of 2 years in 10 patients, and by the age of 6 years in four patients. All patients had worn hearing aids since this time and had intelligible speech. Audiograms were typical with a sloping moderate to severe pattern of high frequency hearing loss which was reported by eight patients to be stable. Some deterioration was felt to have occurred in

six patients. In two cases this was not supported by previous audiograms. Old audiograms in other cases were not available for comparison. We have verified non-progression in a third (case 26) after a period of 7 years. Vestibular function was tested in 10 patients and was normal in nine. In case 7 with a negative caloric test, a more comprehensive vestibular examination is planned.

ERG was extinguished or profoundly reduced in all cases. Pigmentary degeneration was typical for retinitis pigmentosa with peripheral bone spicule pigmentation. One case showed pigment mottling, but no bone spicules, and in one case fundal appearances were suggestive of retinitis punctata albescens. Mild posterior subcapsular lens opacities were seen in three patients, and one patient was pseudophakic, with cataracts removed at 41 years. Reduced acuity was associated with lens opacities and in no patient was less than 6/18.

ATYPICAL PATIENTS (PROBABLY US 3) (TABLE 6)

Six index patients were typed as US 3. Four of six have been clinically reassessed in an ophthalmic department and in two medical records were evaluated. These patients are

Table 5 Patients with Usher syndrome 2—clinical information

| No | Age/sex | Age/diag deafness | Audiogram | Vestibular function | Age diag RP (years) | Age visual symptom (years) | VA | ERG (mV) | Cat | Field (°) | Pigment degen |
|-----|---------|-------------------|------------------|---------------------|---------------------|----------------------------|------|----------|---------------------|-----------|------------------------------|
| 1* | 34/M | 18 months | Sloping mod/sev | + | 35 | 32 | 6/6 | <75 | no | 35 | Moderate |
| 5* | 71/F | 2 years | Sloping profound | ++ | 17 | 15 | 6/9 | ext | no | 10 | Moderate |
| 7* | 39/F | 6 years | Sloping mod/sev | neg | 21 | 10 | 6/9 | ext | no | 15 | Moderate |
| 9 | 56/M | Infant | Sloping mod/sev | NP | 38 | 20 | 6/12 | ext | early PSLO | 10 | Moderate |
| 13* | 36/M | Infant | Sloping mod/sev | ++ | 25 | 15 | 6/9 | ext | no | 10 | Extensive |
| 15 | 16/F | 5 years | Sloping mod/sev | NP | 13 | none | 6/6 | <75 | no | full | Normal fundi |
| 17* | 18/M | Infant | Sloping mod/sev | NP | 14 | 12 | 6/12 | <75 | no | moderate | Moderate |
| 19* | 24/M | Infant | Sloping mod/sev | + | 17 | 14 | 6/9 | ext | no | moderate | Moderate |
| 20* | 59/F | Infant | Sloping mod/sev | ++ | 58 | 54 | 6/18 | ext | mod PSLO | 10 | Moderate |
| 21* | 33/F | 6 years | Sloping mod/sev | ++ | 17 | 17 | 6/12 | ext | no | 20 | Moderate |
| 26* | 30/M | 15 months | Sloping mod/sev | ++ | 30 | 22 | 6/6 | <75 | no | moderate | Retinitis punctata albescens |
| 29* | 38/F | Infant | Sloping mod/sev | ++ | 30 | 30 | 6/5 | <75 | no | 15 | Moderate |
| 33* | 45/F | 2 years | Sloping mod/sev | ++ | 43 | 43 | 6/18 | <75 | pseud opha kos mild | 45 | Mild |
| 35 | 30/M | 5 years | Sloping mod/sev | NP | 10 | 10 | 6/12 | <75 | PSLO | 10 | Moderate |

RP = retinitis pigmentosa; NP = not performed; PSLO = posterior subcapsular lens opacities; ext = extinguished; Cat = cataract; diag = diagnosis; pigment degen = pigmentary degeneration; *clinically reassessed.

Table 6 Patients with Usher syndrome 3—clinical information

| No | Age/sex | Age diag deafness | Audiogram | Vestibular function | Age diag RP | Age visual symptom | VA | ERG (mV) | Cat | Field (°) | Pigment degen |
|-----|---------|-------------------|--------------------------------|---------------------|-------------|--------------------|-------|----------------------------|------------|------------------|------------------|
| 2 | 40/M | teens | Progression to corner profound | NP | 36 | 26 | 6/60 | <75 | mild PSLO | mod constriction | RP sine pigmento |
| 3* | 49/M | 14 | Progression sloping mod/sev | ++ | 40 | 20 | 6/9 | ext | no | 10 | Moderate |
| 6 | 54/M | 16 | Progressed to profound | NP | 16 | 16 | no PL | ext | no | ext | Extensive |
| 8* | 52/F | 12 | NR | ++ | 36 | 36 | 6/9 | <75 | early PSLO | 10 | Extensive |
| 31* | 61/F | 5 | Progression sloping mod/sev | ++ | 21 | 13 | 6/12 | ext | mild PSLO | 10 | Extensive |
| 34* | 39/F | 2 years | Progression from mod/sev to NR | ++ | 38 | 38 | 6/6 | mild reduction ERG and EOG | no | full | Moderate |

NR = non-recordable; RP = retinitis pigmentosa; NP = not performed; PSLO = posterior sub capsular lens opacities; ext = extinguished; Cat = cataract; diag = diagnosis; pigment degen = pigmentary degeneration; *clinically reassessed.

atypical but appear to conform to clinical criteria which support a diagnosis of US 3.¹⁴ Bilateral hearing loss was diagnosed between 2 and 16 years. In five of these patients there was strong anamnestic evidence of an earlier progression of hearing loss but owing to lack of audiological information this could not be confirmed. We were able to confirm progression over the past 4 years in one patient.³¹ Some of these patients had late onset of hearing loss, and no apparent exogenous cause to account for their present profound level of hearing loss. Their clinical histories will now be discussed in more detail below.

Case 2

A 40-year-old Pakistani male, born in Pakistan, whose parents were first cousins. He came to the UK aged 10 years and was said to have had normal hearing up to this time. Hearing loss was diagnosed in his teens and he was educated subsequently at a school for the deaf. His hearing loss had progressed to profound across all frequencies with a corner type audiogram. He had successful cochlear implantation surgery in October 1994. Retinitis pigmentosa was diagnosed age 36 years although symptomatic night blindness was described before this. The ERG was <75 mV, and there was marked reduction of EOG. The visual fields were moderately constricted. On ophthalmoscopy he had attenuated arterioles but no pigmentation—that is, retinitis pigmentosa sine pigmento. Pigmentary changes were present at the maculae with best acuity of 6/60.

There were no other affected family members, including two older sibs, with US, pigmentary retinopathy, or deafness.

Case 3

This 49-year-old male was an identical twin with non-consanguineous parents. His twin brother was also affected with US. He had worn hearing aids from the age of 14 years. The index patient felt his hearing loss had progressed but there was no definite evidence from a previous audiogram dated 1990. Audiograms earlier than this were not available. He had normal vestibular function and a sloping moderate hearing loss but we felt the late diagnosis was suggestive of true progression. He had suffered from night blindness since early childhood and loss of visual field

since his 20s. Retinitis pigmentosa was medically diagnosed at age 40. The ERG was extinguished and his fundi showed typical pigmentary degeneration with bone spicule pigmentation. His twin had a history of perinatal birth problems and had learning difficulties. His hearing loss was diagnosed at age 8 years and he had worn hearing aids since then. The audiogram demonstrated a sloping moderate/severe hearing loss; there was no nystagmus on cold caloric test but the Romberg test was negative. Retinitis pigmentosa was diagnosed at age 40 but he was symptomatic in childhood. Ophthalmoscopy showed pigmentary degeneration with bone spicule pigmentation and the ERG was extinguished.

There are no other affected family members with US, pigmentary retinopathy, or deafness.

Case 6

A 54-year-old white male with consanguineous parents. He had late onset of deafness at age 16 and was fitted with hearing aids when aged 18 years. He had suffered from symptomatic night blindness since the age of 16, and was medically diagnosed as having retinitis pigmentosa when aged 27 years. There had been progressive visual deterioration to total blindness by age 38 years. He had a non-recordable ERG and his visual fields were extinguished. His hearing loss had progressed to profound across all frequencies. Previous audiograms were not available for review. He had been extensively investigated for a progressive sensory polyneuropathy since he was 38 years old and this condition has been stable for the past 2 years. Refsum's syndrome and mitochondrial mutation had been excluded.

There are no other affected family members with US, pigmentary retinopathy, or deafness. Two older sibs are unaffected.

Case 8

A 52-year-old female with no parental consanguinity. Hearing loss was diagnosed at 14 years but she did not wear an aid until she was 36. She attended a normal school. Thresholds were non-recordable on audiometry testing. Previous audiograms were not available for comparison. Vestibular function was normal. Retinitis pigmentosa was diagnosed at age 36 years. The fundus showed typical bone spicule pigmentary degeneration, and there was

profound reduction of the ERG. Visual fields were reduced to 10 degrees. Early cataract was diagnosed in 1994.

Case 31

A 61-year-old female with no parental consanguinity. Hearing loss was diagnosed at age 5 years and she had worn a hearing aid since she was 16. She felt her hearing had deteriorated. Comparison with the only available audiogram 4 years previously showed progression of hearing loss mainly in the low frequency range which is not characteristic of age related hearing loss. Other causes of hearing loss were excluded. Nyctalopia was present from age 13 years and retinitis pigmentosa was medically diagnosed when she was aged 21. The fundi showed extensive pigmentary degeneration, the visual fields were constricted to 10 degrees, and the ERG was extinguished.

Case 34

A 39-year-old female with no parental consanguinity. Hearing loss was diagnosed at age 2 years. She remembered hearing well until about age 14 years. Audiogram showed non-recordable thresholds. She had normal speech. Retinitis pigmentosa was diagnosed at age 38 years when she saw an ophthalmologist because her brother had then been diagnosed with US. Ophthalmoscopy showed typical but mild pigmentary degeneration with bone spicules and arteriolar attenuation. The ERG was mildly reduced and visual fields were moderately constricted.

GENETICS

Genetic data were available from 30 of 31 pedigrees. Two pedigrees are considered separately below as a parent was also affected. In the remaining 28 pedigrees, there were 96 sibs of index patients, of whom 78 were normal, and 18 had Usher syndrome, or rather 17 if we count two affected identical twins as one patient. Thirteen of these 17 secondary cases were ascertained independently of the index patient, and therefore 41 patients (28 index patients, 13 secondary cases) were classified as probands for the purpose of genetic analysis.³² The probands had a total of 178 sibs, of whom 45 were affected. This gives a proportion of 0.25 (2 SE, range 0.17–0.33) which supports the hypothesis of autosomal recessive inheritance.

We consider that the two families (13 and 29), in which a parent was affected to represent the marriage of an Usher patient with a carrier in the parental generation. This would not be surprising in view of the high prevalence of the condition. Case 13 (sib 3 in this family) was from a highly consanguineous Pakistani family from Kashmir with four unaffected siblings, an affected father resident in Birmingham, and three other affected relatives living in Pakistan. Case 29 with non-consanguineous parents had one unaffected sib, one affected sib, and an affected mother and maternal aunt living in Birmingham.

Parental consanguinity was reported in four families (cases 2, 6, 13, and 28). The parents of

case 2 were Pakistani and first cousins, the parents of case 6 were white and second cousins. Case 13 has been described above.

Discussion

The prevalence of US observed in our study of 6.2 per 100 000 population is higher than that found in previous population studies. If atypical cases (probable US 3) are excluded the prevalence of US 1 and 2 is 5.3 per 100 000 population (see Table 3).

We have selected patients only because they were resident in Birmingham in 1994. Review of the literature finds a prevalence ranging from 1.8 to 4.4 per 100 000.^{18–22} Nuutila¹⁸ attempted to make a complete ascertainment of patients in the whole population of Finland over 10 years of age, and found a prevalence of 3.5 per 100 000; however, the disease was very unevenly distributed with a prevalence of 21 per 100 000 in the north where there are geographically isolated groups, and no cases in Helsinki where a tenth of the population were living at the time. Other studies have focused on retinitis pigmentosa populations,^{19 20 23 24} or in schools for the deaf.^{22 25–29} The highest previous prevalence estimate of 4.4 per 100 000 in the USA was considered to be conservative.²¹

We chose to exclude children under 15 years of age where ascertainment is incomplete owing to late presentation of children with symptomatic retinitis pigmentosa and the fact that children are not routinely screened by an ophthalmologist. Although studies have shown that ERGs may be subnormal in infancy,³³ a normal ERG at this age does not rule out the diagnosis of US.⁵ Since it is not yet established at which age US can be safely excluded by ERG and fundus examination, timing of screening programmes becomes problematical. By 15 years we have presumed that most children who have US will be symptomatic, have an abnormal ERG, or have evidence of pigmentary changes on fundus examination.

Our higher prevalence may reflect a more complete ascertainment of cases, at least among young patients because the City of Birmingham Education Department documents all children with special educational needs, and because all patients from Birmingham with symptoms relating to the retinal dystrophies are seen in one department, (the vision function unit of the BMEH). We were not surprised to find a lower prevalence among older patients who will usually not be making regular attendances to clinics for visual or auditory impairments. Therefore, we consider our ascertainment may be incomplete in the group aged over 70 years when patients tend not to be under ophthalmic review. The true prevalence may be reflected more accurately in the 30–49 year age group of 9.5 per 100 000 population.

The different ethnic groups of our patients were in similar proportions to those within the city.

Earlier studies of the profoundly deaf estimated the respective proportion of US 1 and US 2 to be 90% and 10%.^{18 34} However, we have found a high proportion of US 2 patients

in our study which is consistent with data from Fishman and colleagues^{3 17} and Grondahl and Mjoen²⁴ and was even observed in Usher's original report that 19 of his 69 patients with retinitis pigmentosa had 'some degree of deafness' while 11 had deaf mutism (unintelligible speech).² Fishman's group found 71 patients out of 106 to have US 2.¹⁷ Grondahl and Mjoen, in their Norwegian study, found the distribution of US subtypes in 18 probands selected from 89 probands with tapetoretinal degeneration was US 1 eight probands, US 2 seven probands, and US 3 three probands.²⁴ These differences may reflect differences in ascertainment. Hallgren ascertained most completely for deaf patients.³⁴ It is likely that studies which focus on schools for the deaf will underestimate US 2, since their degree of hearing loss allows normal schooling, whereas schools and programmes for the visually impaired and ophthalmic clinics will have a relatively higher proportion of US 2.

US 3 is distinguished from US 2 by the progressive nature of its hearing loss and the later onset of deafness. In the Finnish study, 40% of US patients were found to have progressive hearing loss confirmed in 13% (n = 30) by follow up audiological data.¹⁴ Hearing impairment was diagnosed before the age of 10 years in 60%, between 10 and 20 in 27%, and between 20 and 40 years in 13%. There was no difficulty in distinguishing US 3 hearing loss from age related hearing loss on the basis of its greater degree, and the equal distribution across all frequencies compared with a predominantly high frequency age related loss. Reports of slowly progressive hearing loss in US 2 are not infrequent. This may be due to the normal process of aging in some patients, or be only an apparent loss in some patients with US 2 whose loss in visual ability affects communication skills.

The absence of previous audiological information makes the distinction between US 2 and US 3 difficult in our patients. However, we have classified six atypical index patients as having US 3 (and one twin sibling) since their history and/or clinical findings strongly support this diagnosis (see case histories). The late onset of hearing loss in cases 2, 3, 6, and 8 was inconsistent with a diagnosis of US 2. Case 61 has documentation of progression which is not characteristic of age related loss. Case 34 now has non-recordable thresholds but she did not require hearing aids until 14 years of age. No other diagnosis easily explains the combination of progressive deafness and retinitis pigmentosa in these patients once Refsum's disease has been excluded.

Case 7 (US 2, Table 5) was atypical because cold caloric testing was negative. This patient otherwise was typical for US 2 with intelligible speech, a sloping non-progressive moderate to severe hearing loss, and negative Romberg and Unterberger balance tests. We have decided to classify this patient as US 2 but further vestibular function tests are planned.

It was our initial intention to assess patients with a view to suitability for cochlear implantation. Studies have documented the improve-

ment of auditory perception in the majority of adult postlingually deaf patients but it is felt that generally poorer results in prelingually deaf adults do not justify implanting in these patients. In one study US 1 patients reported considerable advantages in hearing abilities and social life following implantation.³⁵ US 2 patients are not usually considered for implantation because their level of hearing loss is both milder and stable. Patients with true progression may represent a group suitable for consideration for cochlear implants in view of their inevitable loss of visual function. Case 2 in the US 3 group has benefited from such cochlear implantation surgery.

Pigmentary retinopathy was typical in all our patients and did not correlate with any specific subtype. Our impression was that US 1 patients had more extensive fundus involvement. Atrophic foveal lesions were only identified in US 1 patients and these three patients were older than others in this group. Because we did not undertake fluorescein angiography more subtle foveal lesions may have been overlooked. Patients with cataracts were identified in all groups and appeared to be age related. There was no evidence of different subtypes occurring within the same families.

Psychiatric disturbance in US 1 patients has been noted in this and other studies,^{16 18 34} but was specifically noted to be absent in the study of Fishman *et al.*³ This includes schizophrenia-like disorders, atypical psychoses, recurrent depression, and mental retardation and may be related to the loss of both of the two major senses. In our series, four US 1 patients were under psychiatric review with one on treatment for schizophrenia, and three with depressive-type illnesses. The association of psychiatric disorders in our series is to be further evaluated.

In summary, we have found a higher prevalence of Usher's syndrome than previously reported together with a greater proportion of US 2 and US 3 subtypes.

- 1 Von Graefe A. Exceptionelles Verhalten des geichtsfeldes bei Pigmententartung der Netzhaut. *Von Graefes Arch Ophthalmol* 1858;4:250-3.
- 2 Usher CH. On the inheritance of retinitis pigmentosa with notes of cases. *Roy Lond Ophthalmic Hosp Rev* 1914;19:130-336.
- 3 Fishman GA, Kumar A, Joseph ME, Torok N, Anderson RJ. Usher's syndrome. Ophthalmic and neuro-otologic findings suggesting genetic heterogeneity. *Arch Ophthalmol* 1983;101:1367-734.
- 4 Kimberling WJ, Moller CG, Davenport SLH, Lund G, Grissom TJ, Priluck I, *et al.* Usher syndrome: clinical findings and gene localisation studies. *Laryngoscope* 1989;99:66-72.
- 5 Smith RJH, Berlin CL, Hejtmancik, JF Kimberling WJ, Lewis RA, Moller CG, *et al.* Clinical diagnosis of the Usher syndromes. *Am J Med Genet* 1984;50:32-8.
- 6 Kaplan J, Gerber D, Bonneau D, Rozet JM, Delrieu O, Briard ML, *et al.* A gene for Usher syndrome type I (USH1A) maps to chromosome 14q. *Genomics* 1992;14:979-87.
- 7 Kimberling WJ, Moller CG, Davenport S, Priluck IA, Beighton PH, Greenberg J, *et al.* Linkage of Usher syndrome type I gene (USH1B) to the long arm of chromosome 11. *Genomics* 1992;14:988-94.
- 8 Smith RJH, Lee EC, Kimberling WJ, Daiger SP, Pelias MZ, Keats BJB, *et al.* Localisation of two genes for Usher syndrome type I to chromosome 11. *Genomics* 1992;14:995-1002.
- 9 Weil D, Blanchard S, Kaplan, Guilford P, Gibson F, Walsh J, *et al.* Defective myosin VIIA gene responsible for Usher syndrome type 1B. *Nature* 1995;374:60-1.

- 10 Gibson F, Walsh J, Mburu P, Varela A, Brown KA, Antonio M, *et al.* A type VII myosin encoded by the mouse deafness gene shaker-1. *Nature* 1995;374:63–4.
- 11 Kimberling WJ, Weston MD, Moller C, Davenport SLH, Shugart YY, Priluck IA, *et al.* Localisation of Usher syndrome type II to chromosome 1q. *Genomics* 1990;7:245–9.
- 12 Lewis RA, Otterud B, Stauffer D, Lalouel J, Leppert M. Mapping recessive ophthalmic diseases: linkage of the locus for Usher syndrome type II to a DNA marker on Chromosome 1q. *Genomics* 1990;7:250–6.
- 13 Piekte Dahl S, Kimberling WJ, Gorin MB, Weston MD, Furman JMR, Pikus A, *et al.* Genetic heterogeneity of Usher syndrome type II. *J Med Genet* 1993;30:843–8.
- 14 Pakarinen L, Karjalainen S, Simola KOJ, Laippala P, Kaitalo H. Usher's syndrome type 3 in Finland. *Laryngoscope* 1995;105:613–7.
- 15 Sankila EM, Pakarinen L, Kaariainen H, Aittomaki K, Karjalainen S, Sistonen P, *et al.* Assignment of an Usher syndrome type III (USH 3) gene to chromosome 3q. *Hum Mol Genet* 1995;4:93–8.
- 16 Moller CG, Kimberling WJ, Davenport SLH, Priluck I, White V, Biscione-Halterman K *et al.* Usher syndrome: an otoneurological study. *Laryngoscope* 1989;99:73–9.
- 17 Piazza L, Fishman GA, Farber M, Derlacki D, Anderson RJ. Visual acuity loss in patients with Usher's syndrome. *Arch Ophthalmol* 1986;104:1336–9.
- 18 Nuutila A. Dystrophia retinae pigmentosa-dysacusis syndrome (DRD): a study of the Usher or Hallgren syndrome. *J Genet Hum* 1970;18:57–88.
- 19 Amman F, Klein D, Franceschetti A. Genetic and epidemiological investigations on pigmentary degeneration of the retina and allied disorders in Switzerland. *J Neurol Sci* 1965;2:183–96.
- 20 Grondahl J. Estimation of prognosis and prevalence of retinitis pigmentosa and Usher syndrome in Norway. *Clin Genet* 1987;31:225–264.
- 21 Boughman JA, Vernon M, Shaver KA. Usher syndrome: definition and estimate of prevalence from two high risk populations. *J Chron Dis* 1983;36:595–603.
- 22 Tamayo ML, Bernal JE, Tamayo GE, Frias JL, Alvira G, Vergara O, *et al.* Usher syndrome: results of a screening program in Columbia. *Clin Genet* 1991;40:304–11.
- 23 Boughman JA, Fishman GA. A genetic analysis of retinitis pigmentosa. *Br J Ophthalmol* 1983;67:449–54.
- 24 Grondahl J, Mjoen S. Usher syndrome in four Norwegian counties. *Clin Genet* 1986;30:14–28.
- 25 Vernon M. Usher syndrome—deafness and progressive blindness. *J Chron Dis* 1969;22:133–51.
- 26 Van Rijn PM, Cremers CWR. Causes of childhood deafness at a Dutch school for the hearing impaired. *Ann Otol Rhinol Laryngol* 1991;100:903–8.
- 27 Fraser GR. In: *Causes of profound deafness in childhood*. Baltimore: Johns Hopkins University Press, 1976:49–58.
- 28 Fillman RD, Leguire LE, Rogers GL, Bremer DL, Fellows RR. Screening for vision problems, including Usher syndrome, among hearing impaired students. *Am Ann Deaf* 1987;132:194–8.
- 29 Regenbogen L, Godel V. Ocular deficiencies in deaf children. *J Pediatr Ophthalmol Strabismus* 1985;22:231–3.
- 30 Kloepfer HW, Laguaite J, McLaurin JW. The hereditary syndrome of congenital deafness and retinitis pigmentosa. *Laryngoscope* 1966;76:850–62.
- 31 Estimated resident population estimates mid-1994. London: Population Estimates Unit, Office of Population Censuses and Surveys.
- 32 Morton NE. Genetic tests under incomplete ascertainment. *Am J Hum Genet* 1959;11:1–16.
- 33 Young NM, Mets MB, Hain TC. Early diagnosis of Usher syndrome in infants and children. *Am J Otolaryngol* 1996;17:30–4.
- 34 Hallgren B. Retinitis pigmentosa combined with congenital deafness; with vestibulocerebellar ataxia and neural abnormality in a proportion of cases. *Acta Psychiatr Scand* 1959;138 (Suppl):1–101.
- 35 Hinderink J, Brokk J, Mens L, Broek P. Results from four cochlear implant patients with Usher's syndrome. *Ann Otol Rhinol Laryngol* 1994;103:285–93.