Variations in genetic assessment and recurrence risks quoted for childhood deafness: a survey of clinical geneticists

M J Parker, H Fortnum, I D Young, A C Davis

Abstract

We report here the results of a questionnaire survey of consultant clinical geneticists in the United Kingdom to which we had an 81% response rate. In this questionnaire we asked about: (1) the nature of services currently offered to families with hearing impaired children, (2) what recurrence risks they quoted in isolated non-syndromic cases, and (3) what they might suggest for improving the range of genetic services available at present. We noted great variation both in these services and in the recurrence risks quoted in isolated cases. Based on the results of the questionnaire, we have proposed a protocol for the investigation of permanent childhood hearing impairment, which we believe to be both comprehensive and practical in an outpatient clinic setting. It is only by improving existing clinical and social understanding and knowledge of childhood hearing impairment that it will become possible to use recent molecular advances to develop comprehensive and consistent services for these families.

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MRC Institute of Hearing Research, University Park, Nottingham NG7 2RD, UK
M J Parker
H Fortnum
A C Davis

Department of Clinical Genetics, City Hospital, Nottingham, UK
M J Parker
I D Young

Correspondence to:
Dr Parker.

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Recent epidemiological surveys have indicated that the prevalence of permanent childhood hearing impairment (≥40 dB hearing threshold level, averaged over 0.5, 1, 2, and 4 kHz, in the better hearing ear) is approximately 1.3 per 1000 children.[1] Previous studies have indicated that 50% or more of these children have a known genetic aetiology,[2] with the remainder being either environmental in origin or of unknown cause. Approximately 30% of genetically determined hearing impairment is syndromal, that is, associated with other features and falling into a recognised pattern.[3] The remaining 70% is believed to be non-syndromal and to consist of a large number of different entities which cannot be easily distinguished by either clinical or audiological methods.[4–6] At the time of writing, 45 non-syndromal hearing impairment (NSHL) loci have been mapped, 15 dominant (DFNA), 20 recessive (DFNB), eight X linked (DFN), and two mitochondrial. Only five of these genes have so far been cloned.[7] Among these genes, myosin VIIA is particularly worthy of mention as different mutations in this gene can cause Usher syndrome and both autosomal recessive and autosomal dominant non-syndromal hearing impairment.[8] In the last year, the gene encoding connexin 26 (GJB2), a gap junction protein highly expressed in the human cochlea, has been shown to underlie DFNB1.[9] Connexin 26 mutations are now thought to account for up to 50% of prelingual autosomal recessive hearing impairment in white families.[10–12] More specifically, the 30delG mutation has been shown to account for more than 50% of the connexin 26 mutations identified to date and is thought to represent a mutational "hot spot".[11]

Research has indicated that most people with hearing impairment are interested in establishing the cause and the risks of recurrence to close relatives.[13 14] The recurrence risk quoted for a second affected child being born to a healthy unrelated couple who already have one child with non-syndromal hearing impairment is generally based on empirical data. The figure of 1 in 6 which is widely quoted comes from a reanalysis of Fraser's original study[15 16] and independently from a textbook published over 20 years ago.[17] Interestingly, Fraser himself originally suggested an empirical risk of 1 in 10. Subsequent segregation analyses have produced figures of 1 in 10[18] and 1 in 9.[19] In this latter study it was pointed out that the risk estimate approached 1 in 4 with increasing severity of hearing impairment, suggesting a preponderance of autosomal recessive inheritance for profound non-syndromal hearing impairment. It is clearly desirable that some degree of consistency should be achieved across the clinical genetics community when counselling the parents of a child with isolated non-syndromal hearing impairment.

Uniform and standardised criteria for the investigation of the cause of childhood hearing impairment are needed in order to audit and compare services and there is now an increasing understanding that parents put a high priority on obtaining a definitive diagnosis. Recent work has also shown significant diagnostic success when such children are investigated in a systematic manner (N Bulmer, personal communication). The European Working Group on the Genetics of Hearing Impairment has the development of such a protocol as one of its primary remits.[20] Any such protocol has to recognise the importance of drawing a compromise between what is desirable in theory and what is practical in a clinical setting. Fortnum and Davis,[1] in a population based ascertainment study of hearing impaired children, report that 25% of families in Trent were offered appointments

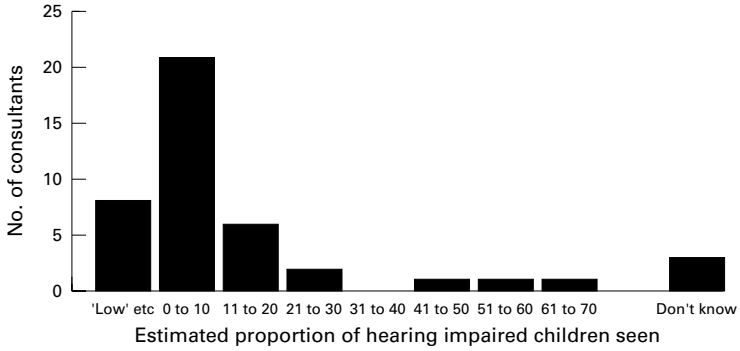

Figure 1 Estimated percentage of local children with hearing impairment seen by individual clinical geneticists.

with a clinical genetics service or someone who gave advice about genetics. They showed considerable variability by district and severity of hearing impairment. However, there were no data on how many families actually attended nor on what such services are actually providing in terms of information to parents or systematic attempts to derive a clearer diagnosis.

In this paper we report the results of a survey of consultant clinical geneticists in the United Kingdom, which attempts to fill in these gaps. We looked to address questions about referral patterns, attendance rates, and local clinical genetics services available for families with a hearing impaired child. In particular, we sought guidance on appropriate routine investigations and information on the spectrum of recurrence risks being quoted for families with a hearing impaired child. Suggestions on how clinical genetics services might be better tailored for these families were also invited.

Methods

Questionnaires were sent by post to 79 consultant clinical geneticists based in all of the known 26 centres in the United Kingdom in June 1997. The questionnaire comprised questions on 11 topics and was designed to be quick and easy to complete. Three months later, one postal reminder was sent to non-responders, stressing that incomplete questionnaires were acceptable and that people should not be deterred from returning questionnaires because of difficulties in obtaining exact figures. The full questionnaire is included as appendix 1.

Results

After two postings, 58 individually completed questionnaires were returned and five other consultants endorsed a collective departmental response. One respondent who no longer undertook any clinical work returned the questionnaire uncompleted. This gives a final response rate of 63/78 (81%). Twenty-six of the 27 known United Kingdom centres were represented in the replies. The total population said to be covered by the 26 centres was approximately 60 000 000, indicating some degree of overestimation or overlap. The mean and median values for individual annual case loads were 500 and 420 respectively. Forty-nine individual respondents provided information about the families referred to them. This enabled us to calculate the proportion of their case load made up of families primarily referred because of hearing impairment. The majority, 47/49 (96%), stated that this proportion was less than 10% and 24/49 (49%) stated that it was less than 2%.

Fifty-five individual respondents provided information about special interest (question 2). Of these, 3/55 consultants (5.5%) specifically mentioned hearing impairment and 23/55 (41.8%) indicated an interest in an area, such as dysmorphology, craniofacial disorders, chromosome abnormalities, and syndrome diagnosis, in which it would be expected that disorders associated with childhood hearing impairment would be encountered. Only two consultants indicated that they would not expect to see children with permanent hearing impairment in their normal practice. In the analyses which follow, the three consultants who stated deafness as an interest have been grouped together with the 23 who had an interest in a related field. Interestingly, these 26 consultants came from only 15 centres, indicating that the other 11 centres (who responded) did not have a consultant who expressed a special interest in deafness or a related field. However, it is recognised that these groupings are somewhat arbitrary as almost all clinical geneticists will encounter disorders in which childhood hearing impairment can occur.

ATTENDANCE RATES

Of the 50 individual respondents who answered the questions about attendance rates (questions 4 and 5 in appendix 1), more than half (n=26) thought that there was no difference between the attendance rate among families with hearing impairment and all other referrals. Of the remainder, 13/50 (26%) thought that families referred primarily because of hearing impairment were more likely to attend and 11/50 (22%) thought that they were less likely to attend.

PROPORTION OF HEARING IMPAIRED CHILDREN SEEN

Forty individual respondents provided information about the estimated percentage of deaf children in their catchment area who were seen by their service. Eight of these respondents made a qualitative statement that the percentage of deaf children that they saw was "low". Of the remainder, the majority (27/32) indicated that they suspected that less than 20% of all children with hearing impairment were seen in their departments (fig 1). There was no significant difference between the estimated percentages of deaf children seen by consultants with (n=19) and without (n=21) an interest in an area associated with childhood hearing impairment.

OTHER PROFESSIONAL GROUPS SEEING FAMILIES FOR GENETIC COUNSELLING

Thirty-five individual respondents indicated that families of hearing impaired children may be receiving "genetic counselling" from other

Table 1 Suggested routine investigations on children

	N=responses
Audiology	
Audiograms	12
ABR (only if NF2 suspected)	1
Virological studies	19
TORCH screen	
Serology (with various age provisos applied)	
Viral investigations (non-specifically)	
Cytogenetic testing	5
Chromosomes (if dysmorphic or developmental delay)	
Fragile X	
Molecular testing	6
(See question on requests for DNA storage and tests)	
Other blood tests	
Haematology	1
U&Es and creatinine	2
TFTs	21
Thyroid autoantibodies	1
Liposomal storage enzymes	2
Other urine tests	12
Urine analysis (variously for blood, protein, oligosaccharides and/or microscopy)	
Ophthalmological assessment	26
Cardiac assessment	
ECG	31
Imaging	
CT/MRI (various provisos, including if male with mixed deafness or X linked pedigree, if profound or progressive or if NF2 suspected)	9
Renal USS	3
CXR	1
Miscellaneous	
Perchlorate discharge test	2
EEG	1

services or groups in their catchment area. The commonest responses were an audiologist or audiological physician (n=18), a paediatrician or community paediatrician (n=13), or a fellow clinical geneticist (n=10). Other services mentioned were ENT (n=4), neurology, education, community physiotherapy, "local network of services", and patient support groups (all n=1). In addition, 20 individual respondents stated that no other services or groups were involved in their locality.

INVESTIGATIONS

Forty-five individual respondents indicated that they would ask for some degree of formal audiological assessment on parents (question 8a), although this was qualified in 16 instances by statements such as "if indicated", "sometimes", and "if there is a positive family history". Fifty-five individual respondents completed question 8b concerning routine investigations on children. Their responses are listed in table 1. The commonest specific investigations indicated were ECG (n=31 respondents), ophthalmological review (n=26), thyroid function tests (n=21), virology for congenital infection (n=19), and other forms of urine analysis (n=12). Imaging (CT or MRI scan) was mentioned by nine respondents, three of whom cited the possibility of X linked inheritance as a specific indication for this.

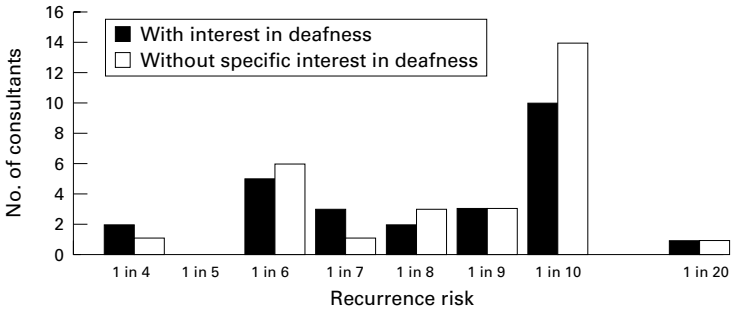

Figure 2 Recurrence risk quoted for unexplained isolated childhood hearing impairment by individual clinical geneticists.

RECURRENCE RISK

Fifty-five people responded to the specific question on recurrence risk (question 9). Where ranges were quoted, the recurrence risk for that particular respondent was taken as the midpoint of the range. The recurrence risks for all respondents are shown in fig 2. The modal responses were 1 in 10 given by 24/55 respondents (43.6%) and 1 in 6 given by 11/55 respondents (20.0%). There was very little difference in the pattern of responses from consultants with and without an interest in an area related to childhood hearing impairment.

REQUESTS FOR PRENATAL DIAGNOSIS AND DNA STORAGE/TESTING

Requests for prenatal diagnosis were generally reported to be limited with most respondents to this question indicating that this was very unusual. Discussions were often not instigated for conditions in which no such tests are available. The few cited examples were for syndromes for which a test had been developed. Some respondents indicated that they suspect that there would be more interest if testing should become available and that some parents would consider this condition to be sufficiently serious to alter their plans for further children. The observation was also made that some hearing impaired parents would prefer to have a child who is also hearing impaired.

Six respondents indicated that they now regularly store DNA from families with non-syndromal hearing impairment. There was also a general consensus that the development of molecular tests for the carrier status in unaffected relatives would be welcomed.

IMPROVEMENTS IN SERVICES

Suggestions for ways in which clinical genetics services could be improved are summarised in table 2. Respondents were not asked to take resource limitations into account. The most common suggestions concerned the need for an agreed protocol for investigation. Closer collaboration with referring specialities was also a recurrent theme as was the setting up of joint clinics. The importance of communication with these families to discover and address their needs was mentioned frequently. There were suggestions that signing interpreters and members of the deaf community could be recruited to help with genetic counselling. The importance of consistency in the provision of a recurrence risk was also recognised.

Table 2 Suggestions for improvements of services

	N=responses
Protocols	
Agreed national protocol for investigation of childhood hearing impairment	14
Liaison	
Joint clinics and better liaison with interested specialities	20
ENT to refer families routinely rather than only if families request referral	2
Education	
Better referral rate through greater awareness of clinical genetic services for such families	6
Increasing teaching about syndromic deafness to relevant groups	3
Targeting	
Person within clinical genetics department with specific interest/expertise	2
Communication	
Genetic associate with special knowledge of the deaf population and communication skills	7
Genetic counsellor for deaf (who signs)	1
'Tests'	
Need for useful molecular tests for non-syndromal deafness, to increase the accuracy of counselling re recurrence risks and improve the options for prenatal diagnosis	8
Improved early diagnosis re cochlear implants	1
Provision for performing parental audiograms at same time as children's ones in audiology	1
Availability of MRI scanning for the investigation of deafness	1
Counselling	
Consistent recurrence risks	1
Preconceptional counselling should be available	1
Patient needs	
Find out what families themselves want	4
Input from genetics departments to schools for hearing impaired	4
By involvement of deaf people to explain about deaf subculture	2

Discussion

CLINICAL GENETICS SERVICES

It is notable that there is almost universal agreement that only a small proportion of families with hearing impairment of genetic aetiology are referred to clinical genetics services. Failure to refer could be for several reasons. Firstly, there could be great variation in the understanding of the significant contribution of genetic factors to permanent childhood hearing impairment. Secondly, there may be limited availability of clinical genetic services in different parts of the country, both geographically and in terms of resources available to each local clinical genetics centre. Finally, there is evidence that not every family with a genetic hearing impairment will welcome contact with a clinical genetics centre. Some groups in the deaf community are disturbed by the recent developments in molecular genetics and their perceived eugenic undertones. Understandably some families may feel stigmatised by the suggestion of an underlying genetic "abnormality" and resent the prevailing medical establishment view that they have an undesirable "disability". Our results indicate that there is widespread awareness among clinical geneticists of the importance of recognising these reservations and treating families with great sensitivity. Involving the deaf community in genetic counselling could help address the concerns of those who have an underlying suspicion of the motives of clinical geneticists.

PROPOSED PROTOCOL FOR INVESTIGATION

A proposed outline protocol for the investigation of childhood hearing impairment, based largely on the results of this questionnaire, is summarised in table 3. Often many of these investigations will be undertaken by other specialists and it could be reasonably argued that the role of the clinical geneticist is to overview and coordinate these investigations to ensure that they are complete. Indeed, the importance of liaison and collaboration between all interested specialities was mentioned by many respondents.

Table 3 Suggested protocol for the aetiological investigation of childhood deafness

Audiology
- Age appropriate, reliable audiological assessment, including tympanometry
  - →child/proband
  - →parents & sibs (if any clinical suspicion of hearing loss)

Urine analysis
- CMV (first 2–3 weeks only)
- Glucose
- Microscopy
- Organic and amino acids

Blood
- Viral serology
  - ⇒rubella (first six months only)
  - ⇒toxoplasma
  - ⇒syphilis
- DNA storage
- Cytogenetic analysis
- T4 & TSH

ECG

Ophthalmological assessment
- ERG

CT/MRI

Vestibular function testing

Perchlorate discharge test

Renal ultrasound scan

This protocol represents a possible minimum standard of investigations which are already available in most centres. Other specific investigations may well be indicated in order to exclude a particular diagnosis in any given family. Investigation of these children should not be seen as a one off event but a continuous process, especially as many syndromal associations are variable in their age of manifestation. Certain tests (notably urine analysis for blood, glucose, and protein, thyroid function testing, and ophthalmological assessment) may well need to be repeated at regular intervals until such time as the responsible clinician can confidently exclude associated pathology in any particular system.

Age appropriate, reliable audiological assessment, including tympanometry to assess middle ear function, is an essential requirement not only for the child, but also for any other hearing impaired family members.

Urine analysis is non-invasive and can be used as an initial screen for several syndromes associated with childhood deafness. Glycosuria may indicate diabetes mellitus as part of the DIDMOAD syndrome, an association of diabetes insipidus, diabetes mellitus, optic atrophy, and deafness. Microscopic haematuria would point towards a diagnosis of Alport syndrome. Urine organic and amino acid analysis is useful when considering a diagnosis of a metabolic disorder, usually indicated by the presence of other suggestive features.

In this proposed protocol, we have deliberately avoided the term "TORCH screen" as there is little value in carrying out an extensive screen for congenital infection unless clinical features point towards a specific infectious agent. Unfortunately, the window of opportunity for making a confident diagnosis of congenital CMV infection is narrow and often missed. The diagnosis can only be confirmed

by isolating the virus from urine within the first one to two weeks of life. Serology is notoriously unreliable as asymptomatic infection is so common.[21] The move towards neonatal hearing screening[22] means that there should be greater opportunity to establish CMV as the cause of hearing impairment.

At present, DNA mutation analysis is available for only a few single gene disorders such as Waardenburg and Alport syndromes. This situation is changing rapidly and if mutations in connexin 26 are found to be as common as initially reported, then mutation analysis of this small gene will almost certainly become part of the recommended protocol for all children with severe unexplained hearing impairment.

Cytogenetic analysis should be performed when there are dysmorphic features or growth/global developmental delay. However, it is not a routinely indicated test in a child with no such features.

Although rare, the Jervell and Lange-Nielsen and the Romano-Ward syndromes are important to identify as they can cause sudden death in the young and an ECG is another simple screening investigation that should be performed as part of the investigation of childhood hearing impairment of unknown aetiology.

All hearing impaired children should be referred for an expert ophthalmological opinion to recognise any pathology that may threaten this other sense that hearing impaired children particularly rely upon. Ophthalmological screening for retinitis pigmentosa as part of Usher syndrome can be performed by means of an electroretinogram and has been reported to be of value even in infancy.[23]

One particular area of uncertainty at present is the role of imaging. This probably reflects the lack of guidance in published reports about the value of CT and MRI scanning in distinguishing the different causes of congenital hearing impairment. In simple terms, CT is the best technique for imaging bony structures. It has no role in establishing whether the hearing impairment is conductive or sensorineural, which is achieved instead by audiological assessment. CT scanning is indicated in a child with a conductive impairment, not attributable to otitis media with effusion, in order to exclude a cholesteatoma or mastoid air cell pathology. MRI scanning is generally the preferred technique for imaging soft tissue, in particular nerves. It is indicated for the identification of nerve hypoplasia or aplasia in children.[24] MRI scanning is also indicated in the investigation of progressive unilateral sensorineural hearing impairment in order to exclude a cerebellopontine angle lesion, such as an acoustic neuroma.

Vestibular function testing is relevant to several syndromal causes of hearing impairment, including Usher syndrome. It has been shown that children with absent vestibular responses do not walk before 18 months of age, so that any child who walks before this age is unlikely to have bilateral vestibular impairment.[25] Formal vestibular assessment is indicated if a vestibular problem is suspected.

Pendred syndrome is an autosomal recessive association of hearing impairment and goitre. Fraser[15] estimated its prevalence to be 7.5% of all congenital deafness, but subsequent studies have disputed this high figure.[26] However, since the recent localisation,[27 28] and indeed now cloning,[29–31] of the causative gene it has been postulated that this condition has been previously underascertained.[30] Reardon *et al*[30] go on to state that 80% of cases of this syndrome have structural cochlear malformations identifiable by computerised tomography (CT). These authors also discuss the role of the perchlorate discharge test which they have shown to be previously underused in the investigation of apparently non-syndromal hearing impairment. They recognise it to be non-specific and difficult to perform in children, but believe it remains "an essential element in the investigation of the singleton deaf child", particularly where structural cochlear malformations are shown on CT scan. Children with Pendred syndrome are usually euthyroid and thyroid function tests are certainly not diagnostic here. However, it is still important to look for the association of abnormal thyroid function with childhood deafness as this may be treated relatively easily.

Structural renal abnormalities detected by ultrasound scanning may well point the way towards the diagnosis of a syndrome where hearing impairment is associated with renal disease, such as branchio-oto-renal (BOR), Alport, and oto-renal-genital syndromes, among others.

RECURRENCE RISKS

Many parents of a child with severe congenital hearing impairment wish to know the likelihood that another child will be similarly affected. At present, counselling for such families is based on empirical recurrence risks. This study has indicated that the range of risks quoted to such parents varies considerably with extremes of 1 in 4 and 1 in 20 and a modal value of 1 in 10. It is rather disturbing that a profession which views as one of its primary roles the provision of accurate information should show such a wide spectrum of opinion and perhaps the time has come for agreement on a consensus figure. One in 10 seems to be the risk which is most widely quoted, and which has a sound basis, so that this would seem to be the figure of choice when presented with an isolated case of unexplained childhood hearing impairment. Even when mutation analysis for genes such as connexin 26 becomes widely available, there will still need to be a level of agreement. Ideally, professionals in different centres in the United Kingdom should be giving similar recurrence risks in families in similar circumstances. This is a subject which is being investigated further through the resources of the Trent Ascertainment Study.[1]

Conclusion

We conclude by drawing attention to the apparent lack of awareness of the role of genetic factors in childhood hearing impairment and suggest that families should have

greater access to existing clinical genetics services. There is evidence of a need for greater collaboration between the specialities involved with these families with agreement on recommended investigations and standardisation of recurrence risks. The continuing isolation of genes which contribute to childhood hearing impairment will simply serve to emphasise the importance of establishing agreed national guidelines and standards.[31]

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Appendix 1: Questions

Name:

(1) What catchment area do you cover (approximate population)?

(2) Please indicate any special interest you have in a particular population group.

(3) Would you expect there to be children with permanent hearing impairment within the population group you see?

If no (you may see only adult cancer referrals, for instance), please go to question 11.

If yes, please continue.

(4) (a) Approximately how many families are you individually referred each year, in total?

(4) (b) What percentage of these families keep arranged appointments (approximate percentage please)?

(5) (a) Approximately how many families are you individually referred each year primarily because of hearing impairment?

(5) (b) What percentage of these families keep arranged appointments (approximate percentage please)?

(6) What percentage of the children with hearing impairment, in the population you cover, do you think you see (approximate percentage please)?

(7) For those children you are not seeing, is there any other service or group that you think they may be seeing for "genetic counselling"?

(8) What investigations (if any) do you routinely carry out when counselling families with a child (or children) with sensorineural hearing impairment: (a) on the parents? (b) on the child?

(9) What recurrence risk would you give to an unrelated couple, who have had one child with non-syndromal sensorineural hearing impairment, with no previous family history or recognised environmental factors?

(10) What experiences do you have of families with children with non-syndromal hearing impairment requesting information about: (a) prenatal diagnosis? (b) DNA storage or tests?

(11) In your opinion, how could clinical genetics services be improved for families with children with hearing impairment?

Any other comments:

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