New Syndrome

Novel Syndrome of Cataracts, Retinitis Pigmentosa, Late Onset Deafness and Sperm Abnormalities: A New Usher Syndrome Subtype With X-Linked Inheritance?

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INTRODUCTION

There are similarities in structural and functional proteins of the inner ear, retina and reproductive tissues; thus shared syndromes are expectable [Khanna et al., 2005]. Hearing loss is a common congenital nonsyndromic finding in live births and is found in more than 400 known syndromic disorders [Morton, 1991]. Usher syndrome is the most frequent deafness-blindness hereditary disorder [Boughman et al., 1983]. The Usher syndromes are a group of autosomal recessive disorders characterized by retinitis pigmentosa (RP), sensorineural hearing loss and variable vestibular abnormalities. There is extensive clinical and genetic heterogeneity in Usher syndrome [Moller et al., 1989]. An X-linked pattern of inheritance had never been documented for a classic presentation of this syndrome (http://webhost.ua.ac.be/hhh). Here we present the characteristic findings in five brothers born from a consanguineous marriage of first cousins, who have almost a uniform presentation of a disorder consisting of progressive late-onset hearing loss, cataracts, RP, sperm shape and functional impairment in the male sibs. While an autosomal recessive pattern of inheritance is possible, the occurrence in five brothers suggests an X-linked pattern of inheritance for this unique condition.

CLINICAL REPORT

The pedigree of the family is shown in Figure 1. The father and mother are 68 and 60 years old respectively and of Kurdish ancestry. Our patients were presented with the chief complaint of late-onset rapidly progressive hearing loss to the Department of Otolaryngology, Head and Neck Surgery. On further investigations, the following signs and symptoms were found in these patients.

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The 38-year-old Patient IV: 3 is the first son (2nd child) from a rather healthy first cousin parents. He has a normal birth history without any perinatal complication or infection. Normal physical and mental development along with normal speech and word generation were confirmed in his clinical investigation. History of trauma, prolonged microbial infection and use of ototoxic drugs had also been ruled out. Endocrinological studies and complete blood count (CBC) analysis were normal. No muscular problem was detected in the patient. Hearing impairment was noted by the patient at the age of 18 years and by 20, he had difficulty hearing sounds in his daily communications. By the age 22, patient could not hear any sound without the use of hearing aids and by 24 years of age, complete deafness had developed. The patient noticed a change in the visual acuity at 28 years of age and after ophthalmological examination, posterior subcapsular (PSC) cataract was diagnosed, and the patient underwent intra-ocular lens (IOL) replacement surgery in October 1999. In January 2006, the ophthalmological consultation reported pigmentary changes compatible with RP (Fig. 2) and the

![Pedigree of the affected family showing the five affected brothers and consanguineous marriage of the parents.](image)

![Retina photos from three brothers. A: Individual IV:3, the oldest brother in whom the pigmentary changes of the retina, optic disc changes and changes in retinal vasculature are becoming evident. B: Individual IV:5, the second brother whose changes are not pathognomonic for the Retinitis Pigmentosa (RP). C: Individual IV:13, the youngest brother who does not have any specific ophthalmologic complaint and recently Posterior Subcapsular (PSC) cataracts had been diagnosed for him with optic disc pallor.](image)
electroretinogram (ERG) test reported decreased amplitude of both a- and b-waves. The patient does not have any complaint of night blindness. He was married at age 22 years to an unrelated individual and currently they have two children who are found to be physically and mentally normal. Figure 3 and Table I summarize the findings in the sperm analysis test of this patient. No response was recorded in his pure tone audiometry (PTA) while vestibular reflexes were found to be normal.

The 36-year-old patient IV: 5 was born without any complication. He does not have any history of prolonged infection. The blood tests and endocrine analysis were normal for this patient. He noted reduction in hearing level at the age of 19 with a progressive nature which resulted in profound deafness at the age of 24. At 30 years of age, he noted some decrease in his visual acuity and during ophthalmological examination, PSC cataract was found in this patient and he underwent an IOL replacement surgery. At the time of our clinical investigation, the ophthalmologist diagnosed pigmentary changes in the retina (Fig. 2). PTA shows profound hearing loss. Vestibular reflexes are normal.
in this patient. After 10 years of marriage and despite willingness to have a child and no use of any contraceptive method by either of the couple, pregnancy had not been successful. Figure 3 and Table I show the result of sperm analysis for this patient with almost all globular sperm without detectable normal shapes.

The 32-year-old third brother has a normal birth history and normal routine laboratory tests. This patient developed hearing loss at the age of 18 and became profoundly deaf by age 23 years. At the time of evaluation, the ophthalmologist reported PSC cataract for this patient and advised cataract surgery. It was noted that the pigmentary changes had begun in the retina. This patient has been married for 7 years and currently has a 4-year-old daughter, and his wife is pregnant. The result of the sperm analysis of this patient in Figure 3 and Table I show enough normal sperm with shape irregularities. PTA reported profound hearing loss in both ears and vestibular reflexes were normal.

The fourth brother is 28 years old and became deaf at the age of 25. The first symptoms of hearing impairment occurred at the age of 19. Vestibular reflexes are normal, but no response was detected in his PTA. Patient has recent reduction in visual acuity. The ophthalmological consultation reported the same PSC cataract together with beginning of pigmentary changes of the retina. This patient has been married for 3 years and by the time of evaluation no evidence of pregnancy or conception was noted despite the willingness of the couple to have a child. The sperm analysis result of this patient is shown in Figure 3 and Table I. This patient has dominantly globular sperm without detectable normal shapes. The blood and endocrine tests of this patient are normal. There is no evidence of prolonged infection or perinatal complications for this patient.

The youngest brother is 27 years old. He has become profoundly deaf at the age of 25. Hearing loss had begun at 19 years of age. Vestibular reflexes are normal in this patient. The ophthalmological consultation at the time of clinical investigations reported PSC cataract, optic disc pallor and macular pigmentary changes (Fig. 2). The ERG shows reduction of the amplitude of both a- and b-waves with a more pronounced change in the a-wave. This patient is not married. The result of sperm analysis as shown in Figure 3 and Table I confirms the existence of enough normal sperm with shape irregularities. Other tests were normal for this last brother.

These patients have also two married sisters, 40 and 34 years old each who have 4 and 3 normal children respectively. Unlike their brothers these sisters have no problem with hearing, vision or fertility. All other tests were normal in the sisters.

**DISCUSSION**

We report on a family with 5 affected brothers whose bilateral deafness started post-pubertal at the age of 18–19 years and quickly progressed into profound deafness within 5–6 years. They all have PSC cataract and RP manifestation, specifically in the two older brothers. RP had not yet become functionally disabling for the patients. There is a spectrum of sperm abnormalities from clinical infertility in two of the brothers to shape and function impairment in the other three. The distinct presentation of symptoms, inclusion of all brothers and consanguinity of parents are all in favor of a hereditary syndromic disorder. The ethnic group of these patients was reported to be rich in genetic studies and comparable to Ashkenazi Jews [Mahdieh et al., 2004; Najmabadi et al., 2005].

The prevalence of ophthalmological disorders is reported to be high in the deaf population reaching
40–60% in different studies [Nikolopoulos et al., 2006]. Hearing impairment and cataract have been reported in some syndromes accompanied by other manifestations not detected in our patients [Heath et al., 2001; Beby et al., 2003; Reddy et al., 2004] and their discrete presentation is reported in few syndromes [Guala et al., 1992]. RP is manifested initially as night blindness and a loss of peripheral vision [Smith et al., 1994]. This had not been a complaint in any of our patients. The X-linked form of RP is well-established [Musarella, 1990; Hims et al., 2003], classically explained [Bird, 1975; Wang et al., 2001] and is currently considered in the genetic counseling of this disease. Since the axoneme is also affected in RP, sperm abnormalities are also found in these patients. Interestingly patients with X-linked RP have primarily sperm abnormalities and reduced motility [Hunter et al., 1988; Connor et al., 1997] but hearing impairment is not found to accompany these manifestations.

PSC lens opacities were reported to be detected in patients with RP, but this finding was inconsistent in these studies and other symptoms of our patients—including sperm abnormalities and hearing impairment—were not found in these reports [Knapp, 1918; Pruet, 1983; Fishman et al., 1985]. A similar syndrome is described in a Scandinavian family with autosomal recessive progressive hearing loss, RP, cataracts and vestibular dysfunction [Rosenberg and Parving, 1996]. The absence of an X-linked inheritance pattern and sperm abnormality in this family, and absence of vestibular dysfunction in our family, makes these two syndromes different.

The most important differential diagnosis for our patients is the Usher syndrome. Usher syndrome is the most frequent cause of hereditary deafness-blindness in humans, presented with sensorineural deafness combined with RP [Boughman et al., 1983]. Three clinical subtypes, USH1, USH2, and USH3, can be defined according to the severity of the hearing loss, the presence or absence of vestibular dysfunction and the age of onset of RP [Petit, 2001]. The most severe form is USH1 that is characterized by severe to profound deafness, balance problem and prepubertal RP. USH2 consists of a stable moderate-to-severe hearing loss, normal vestibular function and loss of vision after puberty. USH3 shows a progressive hearing impairment, variable vestibular dysfunction and RP that can occur at different ages [Smith et al., 1994]. Our family could not easily be classified in any type: USH1 is excluded by post-pubertal RP and normal balance and vestibular reflexes, USH2 by profound hearing impairment and RP beginning in their 30s and USH3 by normal vestibular function and sperm abnormalities as discussed below.

Although the ocular manifestations in the Usher syndrome have overlap in our patients particularly regarding the cataract and macular lesions, one distinguishing feature regarding the RP in our cases is the onset of night blindness which is earlier in Usher syndrome type I [Tsilou et al., 2002]. In some populations, later onset of RP in Usher syndrome is found to be a frequent finding [Grondahl, 1987]. In another study, central vision was reported to be acceptable until mid 30 sec [Fishman et al., 1979] but the sperm abnormality and course of the disorder in our family is not found in these studies. Abnormalities in sperm motility and velocity were detected in Usher syndrome with accompanied tail defects [Hunter et al., 1986] but later sperm analysis of Usher patients in a separate study revealed no major finding in the functional analysis of sperm and no fertility problem was reported in these patients [van Aarem et al., 1999]. In studies on USH1B families from different origins neither a mapping to the X-chromosome nor a case with infertility or sperm function impairment was reported [Adato et al., 1997; Janecke et al., 1999]. Although the sperm abnormality debate is considered mainly in USH1B cases, the onset of RP is considered to be in the first decade of life, a criterion not found in our patients [Tsilou et al., 2002]. Usher syndrome type II is believed to account for more than half of the Usher syndromes [Weston et al., 2000]. It also could have a broader spectrum of phenotypic presentation showing milder forms of RP in some studies [Pieke-Dahl et al., 1993]. USH2 shows normal vestibular responses with the onset of RP later in life usually the second decade [Eudy and Sumegi, 1999]. So far, loci for USH2 are found on chromosomes 1, 3, and 5 and no X-linked inheritance had been reported [Kimberling et al., 1990; Eudy et al., 1998; Hmani et al., 1999; Pieke-Dahl et al., 2000; Weston et al., 2004]. Additionally, other types of Usher syndrome are not reported to be mapped to the X chromosome (http://webhost.ua.ac.be/hhh/).

The shared axonemal structure [Hasson et al., 1995; Liu et al., 1997] explains the presence of other related syndromes with hearing loss, RP, primary ciliary dyskinesia and recurrent respiratory infections [Krawczynski et al., 2004]. Primary ciliary dyskinesia and male infertility is also described [Munro et al., 1994] and more specifically in Kartagener syndrome, infertility, immotile cilia and chronic respiratory infections is reported [Burns, 1979]. About 27 years ago the association of abnormal nasal cilia and RP was described [Arden and Fox, 1979; Fox et al., 1980]. Association between Usher syndrome and bronchiectasis and immotile nasal cilia is also reported [Bonneau et al., 1993], but all of these findings are different from the manifestations in our patients particularly absence of respiratory infections and accompanying sperm abnormalities.

**CONCLUSION**

As discussed, this cluster of manifestations had not been reported previously. Although the Usher syndromes could be considered, the course of the
presentation, accompanying findings, normal vestibular reflexes, associated sperm abnormality and presumed X-linked pattern in the family argue against a straightforward diagnosis of an Usher syndrome. The genetic analysis and linkage study in this family could possibly identify a new locus and a mutation responsible for these findings on the X chromosome. Such investigations are currently planned.

REFERENCES


Usher syndrome type II: Localisation to chromosome 5q.