

Usher syndrome type I associated with bronchiectasis and immotile nasal cilia in two brothers

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Abstract

Usher syndrome type I is an autosomal recessive disease characterised by congenital sensorineural deafness, involvement of the vestibular system, and progressive visual loss owing to retinitis pigmentosa. Here we report the association of this disease with bronchiectasis, chronic sinusitis, and reduced nasal mucociliary clearance in two sibs and we suggest Usher syndrome type I could be a primary ciliary disorder.

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Usher syndrome (US) is an autosomal recessive disease which combines congenital sensorineural deafness and progressive visual loss owing to retinitis pigmentosa (RP).¹ It is considered to be the most frequent cause of deaf-blindness in adults and affects 3 to 6% of deaf children.² Two distinct clinical and genetic subtypes, Usher types I and II, have been described.¹ Usher syndrome type I (USI) is defined by profound congenital hearing impairment with unintelligible speech, vestibular dysfunction, and early onset of RP within the first or at the beginning of the second decade. In Usher type II, deafness is moderate with intelligible speech and RP occurs later. Here we report the association of USI with immotile cilia syndrome in two sibs and suggest this disease could be a primary ciliary disorder.

Case reports

The two brothers (II-1 and II-2, fig 1) were born in 1943 and 1947 to non-consanguineous parents without any family history. They both exhibited the same progression of the disease. Profound sensorineural deafness (120 dB loss)

was diagnosed at the age of 18 months in both of them and they have a total absence of intelligible speech.

Ophthalmic signs were identical in both of them: hemeralopia and visual field loss were first noted before 15 years of age and retinitis pigmentosa was diagnosed on concentric loss of visual field, typical bone spicule on fundal examination, and unrecordable electroretinogram.

Vestibular function was impaired as both had loss of balance; standard caloric testing showed absence of nystagmic responses in the younger patient and was uninterpretable in the older because of spontaneous nystagmus.

In addition, they both had had chronic bronchitis with productive cough from childhood and x rays showed bronchial dilatation predominantly in the lower lobes of the lungs (fig 2) together with maxillary sinusitis.

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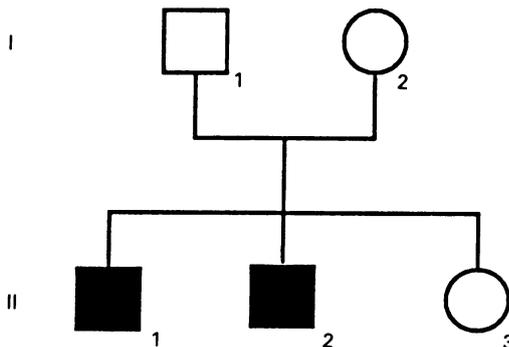


Figure 1 Pedigree of family.

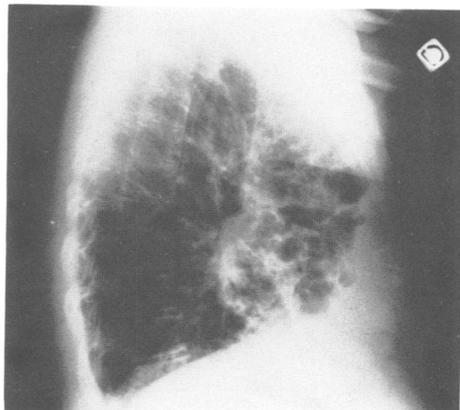


Figure 2 Pulmonar radiographs of II-1 showing bilateral bronchiectasis and normal position of the heart.

Intrathoracic organs were in the normal position.

Nasal mucociliary clearance was assessed using Puchelle's method by measuring the progression of a coloured index placed on the inferior nasal turbinate³; in two consecutive tests progression of the index was less than 10 mm after 20 minutes in both patients (normal = 0.5 to 24 mm/minute).

Electron microscopy of nasal and bronchial biopsies did not show any ultrastructural abnormality of cilia; semen samples for study of spermatozoa velocity and ultrastructure were impossible to obtain.

Discussion

These two brothers exhibited typical Usher syndrome type I, bronchiectasis, chronic sinusitis, and reduced nasal mucociliary clearance. To our knowledge, such an association has not previously been reported and suggests USI could be the result of primary ciliary dyskinesia. This might account for the combined involvement of three different sensory systems since photoreceptors, auditory hair cells, and vestibular hair cells develop from ciliated progenitors.⁴

Several other reports indicate that a generalised abnormality of cilia is present in patients with Usher syndrome. (1) Sperm motility, velocity, and structure have been found to be abnormal.⁴ (2) A high proportion of abnormal axonemes has been found in retinal photoreceptor cells in one patient.⁴ (3) A decrease of outer ciliar cells has been reported at the lower part of the cochlea.⁵ Arden and Fox⁶ have found an increased incidence of abnormal ultrastructure of axonemes in nasal cilia in 11 subjects with retinitis pigmentosa; interestingly, six of their 11 patients were suffering from Usher syndrome.

We have recently proposed that a gene for USI could be located on the long arm of chromosome 14 (q32) for linkage with the DNA probe MLJ14 at locus *DS14S13* (lod

score = 3.20 at $\theta = 0$).⁷ However, further linkage analysis clearly supports the view that US type I is a genetically heterogeneous condition. Heterogeneity test HOMOG allowed us to separate our families into two groups: one linked to chromosome 14 and another one unlinked. Interestingly, eight of the 10 families linked to 14q32 originated from the same area of western France, suggesting a founder effect.⁸ It is of particular interest to note that a mouse gene controlling the position of heart and viscera has recently been mapped to a homologous region to the human 14q32 region,⁹ especially as a normal ciliary function is thought to be required during embryogenesis for normal positioning of the heart and viscera. It is therefore tempting to hypothesise that a relationship could exist between Usher syndrome type I and Kartagener syndrome, especially as cases of Kartagener syndrome have been reported either in association with retinitis pigmentosa¹⁰ or congenital deaf mutism.¹¹

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