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# Is hearing loss a feature of Joubert syndrome, a ciliopathy?

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ABSTRACT

*Objective:* To assess if hearing loss is a feature of Joubert syndrome (JBS), one of the ciliopathies and therefore possibly associated with hearing loss.
*Design:* Retrospective case series.
*Setting:* University Children's Hospital.
*Patients:* Dutch patients with JBS.
*Main outcome measures:* Audiological data.
*Results:* Data from 22 Dutch Joubert syndrome (JBS) cases (17 males, 5 females) aged 3–40 years were available. Audiological tests were successfully performed in 14 cases. Three cases (aged 17–26 years) showed very mild sensorineural hearing loss (SNHL) at different frequencies. Conductive hearing loss due to middle ear infections occurred frequently in young JBS children (6 out of 22 cases). In three cases (aged 3–13 years) the parents reported the child was hypersensitive to sound.
*Conclusion:* We found no evidence for significant hearing loss in Joubert syndrome patients. However, given the compromised speech development in JBS, conductive hearing loss due to middle ear infections should be treated vigorously. SNHL at a later age cannot be excluded on the basis of our data, given the sample size. Three of the older cases showed discretely increased hearing thresholds. Analogous to the ciliopathy Bardet–Biedl syndrome, where hearing thresholds were reported to be subclinically increased in a group of adolescents patients, we recommend follow-up of JBS patients in view of the possibility of progressive, late-onset SNHL.



## 1. Introduction

In otorhinolaryngology, Kartagener syndrome is a well-recognized cause of chronic sinusitis, rhinitis and middle ear infections. The disease is due to a defect of the motile cilia that line the epithelia of the nasopharyngeal tract and ensure mucal transport over the epithelial surface. Recently, increasing attention has been given to another class of cilia, the so-called immotile, primary or sensory cilia. The sensory cilia resemble the motile cilia in structure and localization on the surface of the cell and are important as antennas for extracellular signalling in cell functioning and development. Cilia are present on a large variety of cells. This accounts for the broad range of features in the so-called ciliopathies: from cystic kidney disease, retinal disease, hepatic fibrosis and respiratory tract disease, to mental retardation, cerebellar malformations, neural tube defects, and polydactyly. In accordance with this, there is a large group of genes that regulates ciliary development and functioning; at least 1000 genes have been recognized as part of the ciliary proteome [1].

Primary cilia also play a role in the hair cells of the developing cochlea (see Section 4). It is therefore not surprising that hearing loss is a feature in some ciliopathies. Usher syndrome, characterized by retinitis pigmentosa and congenital or early onset progressive sensorineural hearing loss (SNHL), is a well-known example. Alström syndrome, caused by mutations in the ciliary gene *ALMS1* [2], consists of retinal dystrophy, obesity, diabetes mellitus, and cardiomyopathy. SNHL was reported in 14 out of 22

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**Table 1**
Audiological data of 22 patients with Joubert syndrome.

| Patient | Age/ sex | Reported hearing | Audiometry | Other | DNA analysis *AHI1* | Associated anomalies |
|---|---|---|---|---|---|---|
| 1 | 3/F[a] | Normal, hypersensitivity to sound | Not performed | | Normal | |
| 2 | 5/F | Normal, apart from episodes with MEI[b] | 4 years: bilat. conductive hearing loss (40 dB); 5 years: AD[c] normal, AS[d] 40 dB conductive hearing loss | MEI, tubes | Normal | |
| 3 | 5/M[e] | Normal | 5 years: normal ADS | | Compound heterozygous *AHI1* stop mutations | Retinal dystrophy |
| 4 | 6/M | Normal | Not performed | | Homozygous *AHI1* missense mutation | |
| 5 | 6/M | Normal | 6 years: normal ADS | | Normal | End-stage renal disease |
| 6 | 6/F | Normal, apart from episodes with MEI | 6 years: bilat. conductive hearing loss 20–35 dB | MEI, tubes | Normal | |
| 7 | 8/M | Normal, apart from episodes with MEI | 1 year: conductive hearing loss ADS | MEI, tubes BERA[f] 18 months years normal | Normal | Cystic kidney disease |
| 8 | 8/M | Normal, apart from episodes with MEI | 7 years: normal ADS | MEI, tubes | Normal | |
| 9 | 8/M | Normal, apart from episodes with MEI | Not performed | BERA at age 3 months and 12 months: delayed acoustic nerve development, MEI | Normal | Polydactyly |
| 10 | 8/F | Normal | 8 years: normal ADS | MEI, tubes | Normal | Colobomatous microphthalmia |
| 11 | 10/M | Normal | 10 years: normal | BERA 4 years: normal | Compound heterozygous *AHI1* stop mutations | Retinal dystrophy |
| 12 | 10/M | Normal | 3 years: not valid due to inattention | | Normal | |
| 13 | 13/M | Hypersensitivity to sound, normal hearing | Not performed | | Normal | Hepatic fibrosis, polydactyly |
| 14 | 13/F | Hypersensitivity to sound, normal hearing | Not performed | | Normal | |
| 15 | 15/M | Normal | 10 years: normal | OAE[g] 10 years: normal | Normal | Polydactyly |
| 16 | 17/M | Normal | 17 years: very discrete perceptive HL[h] (10–15 dB), AD 0–4 kH, AS 0–8 kH | | Compound heterozygous *AHI1* stop mutations | Retinal dystrophy |
| 17 | 18/M | Normal | 18 years: AS normal, AD perceptive HL 15 dB at 0.5–2 kH | BERA at age 6 months: normal | Normal | End-stage renal cystic disease, retinal dystrophy |
| 18 | 21/M | Normal | Not performed | | Homozygous *AHI1* Arg830Trp polymorphism | |
| 19 | 26/M | Normal | 26 years: AD normal, AS discrete HL (35 dB) at 8 kH | | Normal | Polydactyly |
| 20 | 32/M | Normal | 26 years (screening at 20 dB for different frequencies): ADS normal | BERA at age 6: abnormal responses (brainstem dysfunction) | Normal | |
| 21 | 32/M | Normal | Data not available; reported normal | | Heterozygous *AHI1* Arg830Trp polymorphism and UV | End-stage renal cystic disease |
| 22 | 40/M | Normal | As a child: 40 dB conductive hearing loss. At age 40 normal | Conductive hearing loss as a child due to MEI | Homozygous *AHI1* missense mutations | Retinal dystrophy |

All patients fulfilled the diagnostic criteria for Joubert syndrome.
[a] Female.
[b] Middle ear infections.
[c] Right ear.
[d] Left ear.
[e] Male.
[f] Brainstem-evoked response audiometry.
[g] Oto-acoustic emissions.
[h] Hearing loss.