

# Familial aggregation of streptomycin ototoxicity: autosomal dominant inheritance?

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**SUMMARY** Eight members of a large kindred of mixed ancestry from a remote rural area of South Africa were investigated for deafness. In each, severe permanent perceptive hearing loss had developed during antituberculous therapy with streptomycin sulphate in conventional doses. Although unproven by the data available in this study, the familial aggregation and pattern of distribution of sensitivity to streptomycin suggested autosomal dominant inheritance.

Streptomycin sulphate is frequently administered routinely as a primary drug in the treatment of pulmonary tuberculosis. The serious ototoxic effects of this drug which occasionally develop are related to the dosage, blood concentration, age of the patient, and renal function. Clustering of untoward reactions within families treated with conventional doses of streptomycin has been noted and in some instances this predisposition has apparently been inherited.<sup>1–3</sup>

We have investigated a large kindred in which eight persons developed severe perceptive deafness during antituberculous therapy with parenterally administered streptomycin sulphate. Our findings are presented and discussed in this paper in order to support the concept of a rare autosomal gene which confers a high risk for a dominant phenotype of permanent perceptive deafness upon exposure to conventional treatment with streptomycin.

## **Investigation, subjects, and methods**

A large non-consanguineous family of mixed ancestry in which several persons had deafness that was related to antituberculous therapy was seen in a peripheral genetic clinic. The kindred consisted of persons of social class V and numerous members had suffered from pulmonary tuberculosis.

The deaf persons in the family, eight in all, were admitted to Groote Schuur Hospital, Cape Town, for appraisal and investigation. A previous history of ear

trauma or infection, renal dysfunction, and specific diseases such as mumps and meningoencephalitis was sought. Specific enquiry was made concerning the time of onset of deafness, tinnitus, and vertigo in relation to tuberculosis treatment. Details of drugs, dosages, and duration of administration were obtained from records at the community treatment clinic.

Routine clinical examination was performed and any concurrent medical conditions were treated. The following special tests of hearing and vestibular function were undertaken: pure tone and speech discrimination tests; tympanometry; the Carhart or Jerger tone decay test; Luschers recruitment test; Bekesy audiometry; electronystagmographic assessments of spontaneous and positional nystagmus; pendulum tracking tests; and the Hallpike bithermal (caloric) induced nystagmus tests.

Several other members of the kindred had retained normal hearing despite antituberculous therapy. For logistical reasons, these persons could not all be brought to Cape Town for investigation. However, every endeavour was made to secure information concerning key subjects.

## **Results**

The pedigree of the kindred is illustrated in the figure. This shows four generations in which eight persons became deaf while on antituberculous therapy. Five additional family members received antituberculous treatment with no apparent effect on hearing, although only one of these (III.50) was given

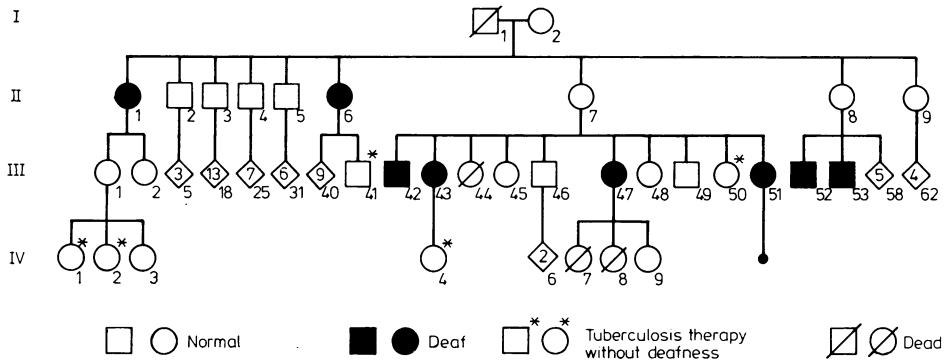


FIGURE Pedigree of affected family.

streptomycin. Both sexes are involved and the pattern of transmission is compatible with, but does not prove, autosomal dominant inheritance.

Basic information concerning the deaf persons is listed in table 1. This includes age at start of treatment, sex, drugs administered together with dosages, duration of therapy, and total dosage, and time and mode of onset of symptoms. It is noteworthy that six of the eight patients were adolescents or young adults when they were treated, while one patient was 6 years of age and the other 49 years of age.

The dose of streptomycin sulphate received by affected persons ranged from 13.0 to 20.0 mg/kg body weight daily. Therapy details are incomplete for three patients but, as far as could be ascertained, none received an amount in excess of 20 mg/kg body

weight per day. (Dose related ototoxic side effects are known to increase markedly above this level.) Total dosages of streptomycin administered averaged 75.5 g per patient in the five subjects for whom accurate records were available.

Those patients with hearing loss (table 2) had bilateral moderately severe to very severe sensorineural deafness, although in four persons the involvement differed in degree between the ears. The speech audiometry results were poor in all these patients, with only five ears attaining word discrimination scores of over 60% at optimal intensity.

The tympanograms were normal, as would be expected from the normal clinical and otoscopic findings in all patients, except in III.43 (patient 4) who had a large perforation of the left tympanic

TABLE 1 Basic data concerning the deaf patients.

Patient No	Pedigree No	Age (yr)	Sex	Therapy	Dosages			Onset of symptoms after start of therapy	Symptoms
					Daily	mg/kg	Total		
1	II.1	25	F	?STM	NR	—	—	1 week	Deafness and tinnitus
2	III.47	20	F	STM	1 g	18.2	75 g	2 months	Deafness
				PZA	2 g	36.4	270 g		
				INH	400 mg	7.3	82 g		
3	III.42	6	M	?STM	NR	—	—	2 months	Deafness
				Others					
4	III.43	28	F	STM	1 g	13.0	66 g	2-3 months	Deafness and severe tinnitus
				PZA	2 g	26.0	132 g		
				INH	400 mg	5.2	26.4 g		
5	III.53	11	M	STM	0.66 g	18.9	40.3 g	1 week	Deafness and tinnitus
				INH	300 mg	8.6	62.7 g		
				PZA	750 mg	21.4	73.5 g		
				ETHAM	600 mg	17.1	95.4 g		
6	II.6	49	F	STM	1 g	18.9	130 g	5 months	Deafness
				INH	300 mg	7.5	52 g		
				PZA	2 g	37.8	260 g		
7	III.51	13	F	STM	1 g	20.0	66 g	2-3 months	Deafness and tinnitus
				INH	400 mg	8.0	96 g		
				RIF	450 mg	9.0	29.7 g		
				ETH	500 mg	10.0	120 g		
8	III.52	16	M	STM	NR	—	—	1-2 months	Deafness and tinnitus
				Others					

STM = streptomycin sulphate, INH = isoniazid, PZA = pyrazinamide, RIF = rifampicin, ETHAM = ethambutal, ETH = ethionamide, NR = not recorded.

TABLE 2 Audiometric and vestibular function studies.

Patient	Pure tone test		Speech discrimination score (%)		ENG findings (calorics)
	Right	Left	Right	Left	
1	Moderately severe	Severe	60	60	Normal
2	Moderately severe	Moderately severe	50	20	No response to ice
3	Very severe	Very severe	0	0	Not done (uncooperative)
4	Moderately severe	Moderately severe	95	95	Not done (perforation)
5	Moderately severe	Moderately severe	90	90	Normal
6	Very severe	Severe	Nil	45	Normal
7	Severe	Very severe	90	45	Normal
8	Moderately severe	Moderately severe	30	40	Normal

membrane. Tone decay was absent in all except patient III.52 who was profoundly deaf. Recruitment of hearing was demonstrated in three persons, one of whom had a type II Bekesy audiogram, all others having a type I.

Spontaneous or positional induced nystagmus was not identified in any patient and the pendulum tracking test was normal in all. Only one (patient 2) had an abnormal caloric test in which even with ice cold water no responses were elicited.

Two patterns of symptomatology were evident with ototoxic features presenting within one week of the start of treatment in patients 1 and 5, and only after 1 to 5 months in the remainder. No subject complained of vertigo, but five persons experienced tinnitus with simultaneous onset of deafness.

An adolescent girl (IV.1), who was ostensibly deaf and who had received only prophylactic tuberculous therapy with isoniazid 300 mg daily, was found to be malingering and to have normal hearing. She had previously convinced another institution of her hearing loss and had been issued with a hearing aid which she never used.

**Discussion**

The ototoxic complications of all the aminoglycoside antibiotics are well known and similar. The mechanism of ototoxicity at a molecular level is unclear but Spoendlin,<sup>4</sup> in electron microscopic studies of the inner ears of cats, showed that the aminoglycoside antibiotics may act in a manner akin to their antimicrobial action by inhibiting protein synthesis. In animal investigations, Kehonen<sup>5</sup> and Engstrom and Kehonen<sup>6</sup> recognised primary damage by streptomycin to the organ of Corti hair cells followed secondarily by the involvement of the nerve fibres and ganglion cells. This process, which is dose related, has been confirmed in human studies.<sup>7</sup>

The type of deafness in our patients is perceptive and is localised to the end organ (cochlea) as confirmed by audiometry. Also demonstrated were the characteristic initial effects of aminoglycoside

toxicity, namely high frequency hearing loss and relatively poor speech discrimination scores. Interestingly, only one of our patients (III.47, patient 2) had abnormal caloric test responses, despite the evidence that the vestibular apparatus is affected before the cochlea in streptomycin sulphate ototoxicity.<sup>8</sup> However, abnormal vestibular test (ENG) findings have been shown to revert to normal in a significant proportion of patients with vestibular damage of this type.<sup>9</sup>

Although a few reports of deafness attributed to the use of isoniazid, rifampicin, and ethionamide have been reported, the drug most likely to have caused loss of hearing in our patients was streptomycin sulphate. All eight persons received the drug in the dosages recommended for their age and physical status and none had evidence of renal impairment. These deaf subjects all claimed to have had normal hearing before the start of tuberculous therapy, and this fact was confirmed by unaffected family members, medical officers, and clinic nurses.

Although rare, familial aggregation of susceptibility to streptomycin toxicity has been reported by Prazic *et al.*,<sup>1</sup> Podvinec and Stefanovic,<sup>2</sup> and Johnsonbaugh *et al.*<sup>3</sup> A genetic basis is suggested by the observation of Donald and Sellars<sup>10</sup> who encountered a mother and child pair in a study of streptomycin ototoxicity in the unborn child.

As shown in the pedigree (figure), eight persons of both sexes had developed deafness while on anti-tuberculous treatment and three consecutive generations are involved. Only one member (III.50) had similar therapy without deafness ensuing, although four (III.41, IV.1, IV.2, IV.4) received other forms of antituberculous therapy without ototoxicity occurring. Streptomycin therapy had been avoided in these persons when it was recognised by community medical officers that some persons in this family had experienced ototoxic side effects from this drug. The distribution of deaf persons versus those of normal hearing in the treatment group, the male to female ratios, and the apparent generation to generation transmission are consistent with autosomal dominant inheritance of susceptibility to

cochlear damage. Several members of the family with normal hearing have never been exposed to streptomycin and some of these persons may well possess the faulty gene. They cannot, however, be identified and formal pedigree analysis is impossible. Streptomycin ototoxicity is apparently behaving as an autosomal dominant trait in this family, although this cannot be fully proven with the available data.

Although familial sensitivity to streptomycin seems to be well established, it is very rare, as evidenced by the paucity of case reports. This contention is supported by the experience of community physicians who are involved with the treatment of tuberculosis in the local population. Although they are aware of familial propensity, they regard it as a highly unusual event, and it seems that the condition is genuinely rare.

The hearing acuity of affected members of this kindred is unlikely to improve. However, direct benefits have accrued from the investigation, in that each deaf person has been fitted with an appropriate hearing aid and carefully instructed on its use. Indirectly, future generations of this family will benefit in a preventative manner by the avoidance of all aminoglycoside antibiotics. The appropriate antituberculosis authorities have already been notified of our findings and recommendations.

It is possible to speculate that the wide range of individual variability of ototoxic reactions to streptomycin therapy may be related to inherited characteristics of receptors on the cell membrane of the hair cells within the inner ear. There are many possibilities, including variation in the numbers of receptors or the amount and specificity of enzymes at the receptor site. For these reasons, it could be postulated that familial streptomycin sensitivity is directly related to the membrane characteristics which are under genetic control.

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