Phenotypic variation in LADD syndrome

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SUMMARY A mother and son are reported with chronic dacryocystitis, cup shaped ears, hearing loss, abnormal teeth, and poor formation of saliva and tears. They are similar to previously reported cases of lacrimo-auriculo-dento-digital (LADD) syndrome. The variability of expression of this autosomal dominant syndrome is discussed, and it is suggested that poor saliva and tear formation be added to the phenotype.

LADD syndrome was first delineated by Hollister *et al* in 1973 in a report of a Mexican father and five of his eight children.¹ Features included nasolacrimal duct obstruction with chronic dacryocystitis, absent lacrimal puncta, cup shaped ears, hearing loss, peg shaped teeth with enamel hypoplasia, various preaxial digital abnormalities, and clinodactyly. One child had an absent kidney and the father had limited elbow mobility. The single case of 'mesoectodermal dysplasia' described by Levy² probably had the same syndrome. The child had the same lacrimal, auricular, and dental abnormalities; hand abnormalities included hypoplasia of the thumbs and soft tissue syndactyly. The left forearm was shortened and the left radius and ulna were synostosed. In addition, the mouth was chronically dry. Hearing was apparently normal.

A mother and son reported by Shiang and Holmes³ had the same constellation of findings but normally shaped ears. In addition, the son had absence of some salivary glands, severe hypertension associated with renal anomalies, limited elbow movement, and no significant hearing loss.

We present a mother and son with similar features and discuss the variation in the syndrome.

Case reports

CASE 1

The proband (V.1, fig 1), a Caucasian male, was referred to the genetic clinic because of deafness and a family history of hearing loss and was seen at the age of 5 years 5 months. He was born in South Africa after a normal pregnancy at 37 weeks'

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FIG 1 Family pedigree.

gestation, weighing 1785 g. The duration of labour was 2½ hours and delivery was assisted by forceps for breech presentation. There was very little amniotic fluid. He fed poorly and a hiatus hernia was diagnosed at 5 months and treated conservatively. Motor developmental progress was a little delayed; he sat unsupported at 9 months, 'bottom-shuffled' at 11 months, and walked at 2 years. Speech development was severely delayed; by 4 years he was saying only two words. Investigation at that time revealed a bilateral sensorineural hearing loss. Transtympanic electrocochleography gave thresholds of 75 dB in the left ear and 65 dB in the right ear, which represents a moderately severe deafness. Pure tone audiometry at the age of 6 years confirmed these thresholds. He now wears hearing aids and talks in sentences but his speech is unclear.

FIG 2 (a) The proband in infancy, (b) and (c) aged 5½ years.

Intellectual development is thought to be normal. Difficult behaviour and overactivity which began at 2 years of age persist. His general health is good apart from occasional episodes of asthma since 3 years of age. He has never produced tears and produces very little saliva, so that he has to take a drink with dry food in order to swallow. He has a chronic mild purulent eye discharge, noticed mainly after sleep. Although there had been no urinary symptoms, urine analyses, serum electrolytes, and intravenous pyelogram had been done to exclude occult renal disease and were normal. Sweating occurs normally.

On examination the height and weight were on the 3rd centile and the head circumference between the 3rd and 10th centile. The right ear was cup shaped due to an overfolded helix (fig 2) and a hearing aid was worn in the left ear, which was normally formed. The lacrimal puncta were present. The deciduous teeth were small, pointed, and spaced out. There was very little saliva in the mouth. The hands were normal apart from mild clinodactyly of the fifth fingers on x-ray. Pronation and supination of the forearms were normal. The palate, hair, nails, and skin were normal.

CASE 2

The mother of case 1 (IV.1, fig 1), aged 32 years, had a hearing loss first detected in her early childhood. A recent audiogram showed a bilateral, moderately severe, mainly sensorineural hearing loss, maximal at 1 kHz, with a relatively minor conductive element. Like her son, she produces no tears and her eyes are habitually dry and reddened necessitating regular instillation of lubricating

drops. A purulent discharge accumulates chronically in both eyes. She reported that on a previous occasion dye had been instilled in the conjunctival sac of both eyes and none had entered the nose, confirming nasolacrimal duct obstruction. Her teeth were all extracted at 19 years of age because of extensive caries; she reported they were very small. She produces little or no saliva and like her son has to take dry foods with a drink. She sweats normally. On two occasions she had been treated for urinary tract infections diagnosed clinically, but there was no direct proof of urinary infection. Previously, she had been normotensive apart from a transiently raised blood pressure at 30 weeks of pregnancy.

She has had two pregnancies. The first produced case 1 and the second resulted in a stillbirth between 24 and 31 weeks' gestation. Necropsy showed no fetal abnormalities but the placenta contained scattered large infarcts which were presumably the cause of the stillbirth.

On examination, the ears were small. The left ear measured 45 mm (less than the 3rd centile⁴) and was cup shaped with an overfolded helix. The right ear measured 51 mm (3rd centile) and was morphologically normal but prominent (fig 3). The lacrimal puncta were present and the eyes dry and reddened. The mouth was dry. The orifices of Stensen's ducts were visible, and she was edentulous and wore artificial dentures. The hands were normal, as were the elbows, palate, hair, nails, and skin.

The proband's maternal grandmother was examined (III.1, fig 1). She had progressive hearing loss, beginning at 35 years of age. Recent audiometry showed a predominantly sensorineural loss in the left ear and predominantly conductive loss in the

FIG 3 The mother of the proband.

right. She had normally shaped ears, normal teeth and hands, and produced saliva and tears. She reported that three of her sibs (III.2, 3, and 4) had progressive deafness beginning in the mid-thirties and her nephew (IV.2) similarly had onset of deafness in his late forties. Her mother (II.1) and grandmother (I.1) were reportedly deaf from middle life. None of these subjects was said to have any other features of LADD syndrome.

Discussion

We have described a mother and son who both have chronic dacryocystitis, poor tear formation, cup shaped ears, hearing loss of early onset, abnormal teeth, and poor saliva formation. In addition, the son had mild clinodactyly. Other members of the present family (fig 1) had hearing loss which was probably a separate condition from LADD syn-

drome, since the onset was much later and the other features of LADD syndrome were absent.

The mother and son described are similar to two families reported with LADD syndrome and to the child described by Levy² (table). Although our cases lacked significant digital abnormalities, the combination of features, including the salivary gland defect which was also noted previously, lead us to conclude that all three families and the single case² do have the autosomal dominant LADD syndrome, in which there is variation of phenotypic expression.

The main lacrimal abnormalities in previous cases were nasolacrimal duct aplasia or obstruction or absent lacrimal puncta or both, usually associated with chronic epiphora and dacryocystitis. In addition to chronic dacryocystitis in our family, tear production was absent, presumably secondary to aplasia or hypoplasia of the lacrimal glands. Aplasia or hypoplasia of salivary glands probably accounts for absent salivation in our cases and in the case of Levy.² Indeed, absence of the parotid glands was noted in the proband described by Shiang and Holmes³ but not in his affected mother. The variability of the salivary defect in one family argues against this being due to genetic heterogeneity. The cup shaped ears may be unilateral, bilateral, or asymmetrical, as in case 2. Hollister *et al*¹ noted that in one case with unilateral cup ear, the hearing loss was on the same side. In our proband, the cup ear was unilateral but the hearing loss was bilateral. The hearing loss may be predominantly sensorineural or conductive and may be mild or severe. Hearing was normal in two cases.^{2,3} Our proband illustrated the problems of delayed speech development and behaviour disorder which were probably secondary to the delayed diagnosis of severe hearing loss. The dental anomalies in our family, namely small,

TABLE Comparison of cases of LADD syndrome.

Manifestation	Reported cases									Present cases		Total
	Hollister <i>et al</i> ¹						Levy ² Shiang and Holmes ³					
Case No and sex	1 F	2 M	3 F	4 F	5 F	6 M	1 M	1 M	2 F	1 M	2 F	
Lacrimal anomalies												
Nasolacrimal obstruction and/or chronic dacryocystitis	+	+	+	−	−	+	+	+	+	+	+	9/11
Absent lacrimal puncta	+	+	+	−	+	+	+	+	+	−	−	8/11
Absent tears	−	−	−	−	−	−	−	−	−	+	+	2/11
Cup shaped ears	+	(B)	+	(B)	+	(B)	+	(B)	−	+	(U)	9/11
Hearing loss	+	(B)	+	(B)	+	(U)	+	(B)	−	+	(B)	9/11
Dental abnormalities	+	+	+	+	+	+	+	+	+	+	+	11/11
Digital abnormalities	+	+	+	+	+	+	+	+	+	+	+	10/11
Salivary gland abnormalities	−	−	−	−	−	−	+	+	−	+	+	4/11
Limited elbow mobility	−	−	−	−	−	+	+	+	−	−	−	3/11
Renal abnormalities	−	+	−	−	−	−	−	+	−	−	−	2/11

+ = present. - = absent. B = bilateral. U = unilateral. * = unilaterally shortened forearm.

pointed, widely spaced teeth, prone to severe caries, have been found in all cases. The hand abnormality in our family was minimal but other cases have had clinodactyly and various preaxial anomalies, such as duplicated terminal phalanx of the thumb, syndactyly of the second and third digits, preaxial polydactyly, and exaggerated interdigital cleft between the second and third fingers.¹⁻³ Limited forearm supination in three patients, and unilateral forearm shortening in one, led Temtamy and McKusick⁵ to suggest that LARD (lacrimo-auriculo-radio-dental) may be a better name for the syndrome.⁵ The currently accepted acronym is LADD syndrome.⁶ Our case 1 had a low birth weight and continues to grow along the 3rd centile. Mention of height and weight was not made previously and it remains to be seen if small size is part of the syndrome. Renal anomalies (unilateral kidney and nephrosclerosis with hypertension) have been found in two patients.

While the manifestations of the LADD syndrome may all occur as isolated autosomal dominant traits⁶ their combination is unique. The autosomal dominant branchio-oto-renal (BOR) syndrome is similar, with hearing loss, malformations of the pinna, lacrimal duct stenosis, and renal anomalies, but is distinguished from LADD syndrome by auricular pits and branchial fistulae or cysts and absence of dental and digital anomalies.⁷

This report provides further evidence for the association of salivary gland abnormalities with LADD syndrome and suggests that defective tear formation should be added to the phenotype.

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