Lacrimo-auriculo-dento-digital syndrome: A case report and literature review

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Abstract:

We report a healthy 18-year-old male Saudi with bilateral agenesis of the lacrimal puncta and canaliculi associated with large dacryocystocele on the right side without tearing or inflammation, detected in conjunction with other characteristic features of lacrimo-auriculo-dento-digital dysplasia syndrome. Computed tomography scan indicated that dacryocystoceles were bilateral and asymmetrical, with large dimensions at the right side and associated to a right side maxillary sinus mucocele. The right dacryocystocele was surgically removed, and the histology indicated characteristics of the lacrimal sac. The liquid content of the dacryocystocele was negative for microbes. The atypical mucocele in the maxillary sinus disappeared after dacryocystocele removal probably, due to recovery of sinus drainage.

Keywords:

Congenital anomalies, lacrimal drainage system, lacrimo-auriculo-dento-digital dysplasia syndrome

Introduction

Lacrimo-auriculo-dento-digital dysplasia (LADD) or Levy-Hollister syndrome is a very rare mesodermal dysplasia first described by Levy in 1967.[1,2] The disorder can present sporadically or as an autosomal dominant trait, displaying variable expressivity of multiple congenital anomalies.[3,4]

There are around 62 cases already reported in the literature [Table 1],[1-29] with variable phenotypic expression, characterized by bilateral or unilateral lacrimal abnormalities (hypoplasia, agenesis or atresia of lacrimal puncta and canaliculi, dacryocystocele, and nasolacrimal duct obstruction) isolated or combined with lacrimal gland agenesis or hypoplasia (resulting in dry eyes), dental deformities (peg-shaped teeth, microdontia, hypodontia, and enamel dysplasia), major salivary parotid and/or submandibular glands aplasia or hypoplasia (resulting in dry mouth), external ear malformations (low-set and cup-shaped auricles) with or without hearing deficits, skeletal anomalies, especially in the hands, arms, and feet, with preaxial digital abnormalities (hypoplastic thumbs and radii, clinodactyly, and syndactyly).[1-29]

To the best of our knowledge, this syndrome has not yet been reported in the Arabic Peninsula. This particular LADD case was the first to present with a maxillary sinus mucocele with spontaneous resolution after removal of the lacrimal sac mucocele. Hence, the aim of this is to report a case of LADD in a Saudi male with an unusual mucocele affecting the maxillary sinus, the outcomes after treatment, and a literature review.

Case Report

An 18-year-old male Saudi presented to King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia, in 2016 complaining of a slowly progressing cystic lesion located below the right medial canthal ligament with no infectious symptoms. He is a product of an uncomplicated full-term pregnancy, with vaginal vertex delivery. The patient had a normal birth weight and normal development. He denied any medical illnesses, and there is no other family member with a similar problem.

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Table 1: Features and abnormalities in lacrimo-auriculo-dento-digital dysplasia syndrome reported cases in the literature

Author	Gender	Age (years)	Tearing	Secretion	Puncta	NLDO	Ears*	Hearing loss	Dental	Dry mouth[ʊ]	Digital	Renal
Levy, 1967[1]	Male	12	Yes	No	Normal	No	Yes	No	Yes	Yes	Yes	Normal
Hollister *et al*., 1973[2]	Female	15 month	No	Yes	Absent	Yes	Yes	Bilateral	Yes	No	Yes	Normal
	Male	4	Yes	Yes	Absent (2)[†]	Yes	Yes	Bilateral	Yes	?	Yes	Abnormal
	Female	6	Yes	Yes	Absent (1)	Yes	Yes	Bilateral	Yes	?	Yes	?
	Female	11	No	No	Normal	No	Yes	Bilateral	Yes	?	Yes	?
	Female	17	No	No	Absent	No	Yes	Unilateral	Yes	?	Yes	?
	Male (father)	43	Yes	Yes	Hypoplasic	Yes	Yes	Bilateral	Yes	?	Yes	?
Shiang and Holmes, 1977[5]	Male	21	No	Yes	Absent	Yes	No	No	Yes	Yes	Yes	Abnormal + hypospadia
	Female (mother)	?	No	?	Absent	Yes	No	Bilateral	Yes	No	Yes	Normal
Thompson *et al*., 1985[6] (first to describe dry mouth)	Male	5	No	Yes	Normal	Yes	Yes	Bilateral	No	Yes	No	Normal
	Female (mother)	32	No	Yes	Normal	Yes	Yes	Bilateral	No	Yes	No	Abnormal
Hennekam, 1987[7]	Male (+3 family members)	20 month	No	Yes	Normal	?	Yes	No	Yes	No	Yes	Normal
Kreutz and Hoyme, 1988[8]	Female	9	Yes	Yes	Fistula	Yes	Yes	No	Yes	?	Yes	?
	Female	? (mother)	No	No	Normal	No	Yes	?	Yes	?	Yes	?
	Female	Stillborn	?	?	?	?	Yes	?	?	?	Yes	Normal
Wiedemann and Drescher, 1986[3]	Male	30 month	Dryness	?	Absent (1)	Yes	Yes	?	Yes	Yes	Yes	Normal
	Female (mother) (+grandmother)	29	No	Yes	?	?	Yes	Bilateral	Yes	Yes	Yes	Normal
Calabro *et al*., 1987[9]	Female	17 month	?	?	?	?	Yes	?	Yes	?	Yes	?
	Female	26 (mother)	?	?	?	?	Yes	?	Yes	?	Yes	?
Roodhooft *et al*., 1990[10]	Male	10 month	Yes OS	Yes	Absent (2)	?	Yes	No	Yes	?	Yes	Abnormal
Bamfort and Kaurah, 1992[11]	Female (grandmother)	64	No	No	Normal	No	No	Bilateral	Yes	No	Yes	Normal
	Female (mother)	30	No	No	Normal	No	No	?	No	No	No	Normal
	Male	Stillborn	?	?	?	?	?	?	?	?	?	Abnormal
	Female	12	Yes	?	Absent	Yes	No	No	Yes	No	No	Normal
	Female	Stillborn	?	?	?	?	?	?	?	?	Yes	Abnormal
	?	?	Yes	?	Normal	Yes	Yes	No	No	No	Yes	?
	Male	18 month	Yes	?	Normal	Yes	Yes	No	?	?	Yes	Normal
Lacombe *et al*., 1992[12] (mental retardation)	Female	22 months	No	Yes	Absent	Yes	Yes	Bilateral	Yes	?	Yes	?
	Female (mother)	25	No	No	?	No	No	No	Yes	?	Yes	?
Heinz *et al*., 1993[13]	Female	8 month	Dryness	Yes	Absent (2)	Yes	Yes	Bilateral	Yes	No	Yes	Abnormal
	Female (mother)	28	Dryness	Yes	Absent (1)	No	No	Bilateral	Yes	Yes	Yes	Normal
Ostuni *et al*., 1995[14] (ptosis + telecanthus + corneal perforation)	Female	24	Dryness	?	?	?	Yes	No	Yes	Yes	Yes	Normal
Toumba and Gutteridge, 1995[15]	Female	9	Dryness	No	?	?	Yes	No	Yes	No	Yes	?
	Female	20	Dryness	Yes	?	?	Yes	No	Yes	No	Yes	?
	Male	13	Dryness	Yes	?	?	Yes	Yes	Yes	Yes	Yes	?
	Female	3	Dryness	No	?	?	Yes	Yes	Yes	No	Yes	Normal
	Female	?	No	No	?	?	No	Yes	No	No	No	?
	Female	?	Dryness	Yes	?	?	Yes	No	Yes	Yes	Yes	?

Contd...

Table 1: Contd...

Author	Gender	Age (years)	Tearing	Secretion	Puncta	NLDO	Ears*	Hearing loss	Dental	Dry mouth$^{\sigma}$	Digital	Renal
Lemmerling *et al*., 1999[16]	Female	16	?	?	?	-	Yes	Yes	?	?	?	?
Azar *et al*., 2000[17] (epiblepharon + entropion + hypoplastic epiglottis)	Male	5		Yes	Normal	Yes	?	Bilateral	Yes	?	Yes	Abnormal
Meuschel-Wehner *et al*., 2002[18]	Female	13	Dryness	?	Normal	?	No	No	Yes	Yes	Yes	?
Fierek *et al*., 2003[19]	Male	2	Dryness	Yes	?	?	Yes	Bilateral	Yes	Yes	Yes	?
Ramirez and Lammer, 2004[20] (clef lip + palate)	Female	6	No	?	?	?	Yes	No	Yes	Yes	Yes	Normal
	Female	9	No	?	?	?	Yes	Bilateral	Yes	?	Yes	Abnormal
	Female (mother)	?	Yes	?	?	Yes	Yes	Bilateral	Yes	?	Yes	Abnormal
	Female	?	No	?	?	?	No	?	Yes	?	Yes	Normal
	Female	?	No	?	?	?	Yes	?	Yes	?	Yes	Normal
	M	?	No	?	?	?	Yes	?	Yes	?	Yes	Normal
	Female (mother)	?	No	?	?	?	Yes	?	Yes		Yes	Normal
	Female	?	No	?	?	?	No	?	Yes		Yes	Normal
Lehotay *et al*., 2004[21]	Female	13	?	?	?	?	Yes	Bilateral	Yes		Yes	?
Haktanir *et al*., 2005[22]	Male	14	Dryness	Yes	Normal	Yes	?	Bilateral	Yes		Yes	?
Ong *et al*., 2005[23]	Male	15	Dryness	?	Absent	Yes	?	?	?		?	?
Milunsky *et al*., 2006[24] (lacrimal fistula)	Female	3	No	No	Absent	Yes	?	No	Yes		Yes	Normal
	Female	2	Yes	?	?	No	No	No	Yes		Yes	?
Inan *et al*., 2006[4]	Male	13	Dryness	Yes	?	Yes	Yes	Bilateral	Yes		Yes	?
Caluff *et al*., 2009[25]	Male	13	Dryness	No	Normal	No	Yes	Bilateral	Yes		Yes	?
Mathrawala and Hegde, 2011[26] (antimongolian slant)	Male	7	Dryness	Yes	?	Yes	Yes	?	Yes		Yes	Normal
Lim *et al*., 2012[27] (ophthalmoplegia)	Female	5	Dryness	?	?	?	Yes	?	Yes		Yes	?
Santo *et al*., 2013[28]	Female	13	Dryness	Yes	Absent	Yes	?	?	Yes		Yes	?
Pathivada *et al*., 2016[29]	Male	7	Dryness	?	?	Yes	Yes	?	Yes		?	?
Alhamadi *et al*., 2020**	Male	17	Dryness	Yes	Absent	Yes	Yes	No	Yes		Yes	?

*Cup shaped/low set, **Present case, †In parentheses the number of absent puncta, $^{\sigma}$Dry mouth or salivary glands abnormalities. ?: Information not available, NLDO: Nasolacrimal duct obstruction

A very large dilated round nontender cystic mass measuring around 20 mm × 20 mm was located below the right medial canthal ligament and in the lacrimal fossa area, with no regurgitation of secretion on pressure. In the left side, there was no palpable mass in the medial canthus. Bilaterally, the upper and lower puncta and canaliculi were absent and lacrimal lid portion was short. Intercanthal distance was 35 mm and interpupillary distance was 63 mm. The periorbital skin was hyperpigmented bilaterally. The eyelid margins were hyperemic with wet lashes and mucous yellowish sticky discharge in both sides. Schirmer test was 15 mm OD and 13 mm OS. Bilateral instability of the tear film and superficial diffuse punctate keratopathy were noted. Otherwise, the conjunctiva was quiet. Ocular examination indicated bilateral myopia with corrected visual acuity of 20/20 in both eyes, and otherwise, the eyes were normal.

The patient presented with other features including low-set and cup-shaped auricles with normal hearing, small, pointed, and widely spaced teeth, dry mouth, and long phalanges in the hands with hypoplasia of the thumbs. A foot X-ray indicated supernumerary distal left phalanx attached to the base of the deformed big toe and to the head of the fourth metatarsal bone as an abnormal syndactyly fusion [Figure 1].

Computed tomography (CT) scan indicated bilateral dacryocystocele extending inferiorly into the nasolacrimal duct with bilateral enlarged intraosseous portion ending abruptly in a bony obstruction and without entry into the inferior meatus. The right dacryocystocele was very large, and a smaller dacryocystocele was present in the left side. The right maxillary sinus presented with an expansive, cystic lesion with fluid (30 Hounsfield units). The patient had a significantly deviated nasal septum with a large bony spur toward the right side and bilateral *agger nasi* cells. The lacrimal gland was hypoplastic bilaterally but significantly more hypoplastic in the right side [Figure 2]. In the temporal bone, the middle ear ossicles were normal on both sides.

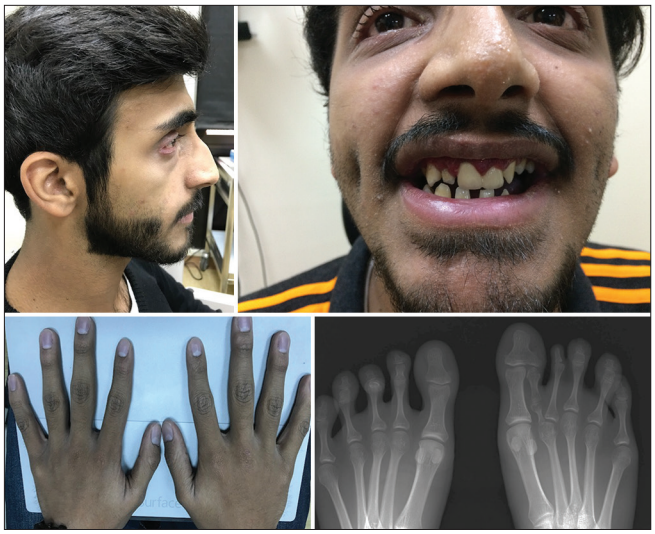

Figure 1: Clinical image after dacryocystocele removal. Sticky secretion in the lashes. Low-set and cup-shaped auricles. Small, pointed, and widely spaced teeth. Long phalanges in the hands with hypoplasia of the thumbs. Supernumerary distal phalanx with abnormal syndactyly fusion with fourth metatarsal bone in the right foot

Magnetic resonance imaging confirmed bilateral distended lacrimal sacs and nasolacrimal duct atresia associated with the bilateral aplasia of the parotid and the submandibular salivary glands and hypertrophied minor salivary glands along the oropharyngeal wall.

Nasal endoscopy confirmed a nasal septal deviation and narrow space in the medial meatus with no intranasal mucocele extension.

The large right dacryocystocele was surgically removed *in toto* and was identified as a large cyst with a smooth wall, containing crystalline secretion, nonadherent to the proximal structures. A swab was taken from the cyst content, and Gomori methenamine silver and acid-fast bacilli were negative for any organisms.

The histologic examination indicated that the cyst wall was composed of pseudostratified columnar epithelium showing mucin-secreting goblet cells, and the submucosal tissue was focally infiltrated with mixed-type chronic inflammatory cells including lymphocytes, plasma cells, and scattered eosinophils. The conclusion was consistent with a normal lacrimal sac and part of the nasolacrimal duct.

In the postoperative period, the patient continued with wet and sticky secretion linked to the lashes. Another CT scan 6 months after right dacryocystocele removal indicated spontaneous regression of the right maxillary sinus abnormalities.

Comments

We report a very rare case of dacryocystocele in a Saudi adult associated with bilateral congenital agenesis of the puncta and canaliculi in the upper and lower lids and other features as ear, dental, and digital abnormalities, compatible with LADD. Despite the fact that most of reported cases had autosomal dominant inheritance, our patient had no previous family history of this condition, likely to be the result of a new mutation in the gene.

Details of the 62 previous reported cases and the percentage of the LADD features are presented in Tables 1 and 2.

Our patient was a male. However, 64% of the reported cases of LADD are female. Our patient presented and was diagnosed for the first time as an adult, but many findings of LADD can be recognizable at birth.

Despite bilateral congenital puncta and canalicular agenesis, our patient did not complain about epiphora. Epiphora is present only in 19.6% of LADD carriers.[1,8,10,11,20,24] The reason for that can probably be attributed to the fact that this syndrome can be associated to lacrimal gland aplasia or dysfunction and acinar hypoplasia[4,5,13,22,28] as we observed also in our patient.

Aplasia or hypoplasia of the lacrimal gland can result in dry eyes, with abnormal lacrimal tear and limbal stem cell deficiency, predisposing to corneal epithelial erosions, neovascularization, and hypoesthesia.[6,14,30]

The chronic sticky secretion in the eyes or the lashes as observed in our patient was detected in many LADD cases.[2-8,10,12,13,15,17,19,22,26,28] It can be related to chronic dacryocystitis or reflecting the instability of the tear film secondary due to lacrimal gland dysfunction.[31]

Our patient had agenesis of the four lacrimal puncta and canaliculus. Underdeveloped or absent lacrimal puncta can be unilateral or bilateral in 45.2% of the LADD cases.[2,3,5,10-13,23,24,28]

Nasolacrimal duct obstruction was detected bilaterally in our patient. Obstruction of the lacrimal ducts can occur in 71.4% of LADD carriers.[2-6,8,11-13,17,20,22-26,28,29] Even with nasolacrimal duct obstruction, acute dacryocystitis never occurred in the present case because the upper lacrimal system was absent and bacteria could not access the cyst. However, chronic dacryocystitis has been reported in LADD cases with patent upper lacrimal excretory system.[4,13,26]

Other less common features of LADD as telecanthus, ptosis,[14] epiblepharon, entropion,[17] lacrimal fistula,[8,24] antimongoloid slant,[26] and ophthalmoplegia[27] were not detected in our patient.

The chief complaint of our patient was a large cystic lesion that was slowly progressive with no episodes of infection. Dacryocystocele in adolescents or adults are extremely rare.[28] LADD dacryocystocele is distinct from congenital dacryocystocele that is noted in general at or within a few days after birth, characterized by the appearance of a cystic blue mass over the region of the lacrimal sac with the possibility of spontaneous resolution and risk of complications due to intranasal mucocele.[32,33]

The cystic lesion was located below the right medial canthal ligament. CT scan documented bilateral dacryocystocele smaller in the left side and bilateral nasolacrimal ducts not developed with a dilated intraosseous portion of the obstructed nasolacrimal duct, which can represent an arrested development in the initial embryonal stages, when only the lacrimal sac was canalized.[23]

The nature of the entrapped fluid inside a dacryocystocele is questionable. The agenesis of the upper lacrimal system makes it unlikely that the external fluid extended into the cyst. The crystalline secretion filling the large dacryocystocele verified during the surgery for cyst removal was likely due to cyst wall production, confirmed by biochemical and histological examination showing lacrimal sac epithelium with goblet cells.

The chronic cystic enlargement of the inferior portion of the right lacrimal system resulted in obstruction of the normal drainage of the maxillary sinus, leading to the development of a mucocele and chronic sinusitis.[28,34,35] Notably, the pathology spontaneously resolved after removal of the lacrimal dacryocystocele.

Other phenotypic characteristics of LADD were present in our patient including the low-set and cup-shaped auricles, which occur in 78.2% of LADD patients.[1-4,6-16,19-21,25,27,29] The malformations of the auricular pavilion can be quite variable, ranging from slight changes to the nonformation of the ear.

Although we did not perform an audiometric assessment to rule out a possible hearing deficit, our patient had no hearing complaints. Auricular pavilion alterations are often accompanied by unilateral or bilateral hearing loss, which can occur in 59.1% of LADD carriers.[2-6,11-13,15-17,19,20-22,25] The changes can be in the inner ear (sensorineural deafness), in the middle ear (conductive hearing loss), or both (mixed hearing loss), and CT scan images can show abnormalities in the temporal ear ossicles, which was not found in our case.

Other features of LADD in our patient included dental anomalies as peg-shaped incisors, microdontia, hypodontia, and enamel dysplasia. Dental anomalies are very common characteristic in LADD disease, present in 91.1% of the cases.[1-5,7-15,17-22,24-29] Hypoplasia or aplasia of salivary glands

Table 2: Number and percentage of lacrimo-auriculo-dento-digital dysplasia characteristics presented in the previously reported cases in the literature

Variable	Yes (%)	No (%)*	Unknown**
Tearing	11 (19.6)	45 (80.3)	6
Secretion	24 (66.7)	12 (33.3)	26
Puncta agenesis	14 (45.2)	17 (54.8)	31
NLDO	25 (71.4)	10 (28.6)	27
Ears	43 (78.2)	12 (21.8)	7
Hearing loss	26 (59.1)	18 (40.9)	18
Dental alterations	51 (91.1)	5 (8.9)	6
Dry mouth	23 (65.7)	12 (34.3)	27
Digital alterations	53 (91.4)	5 (8.6)	4
Renal	23 (69.7)	10 (30.3)	29

*Absent or dryness, **Unknown or not reported. NLDO: Nasolacrimal duct obstruction

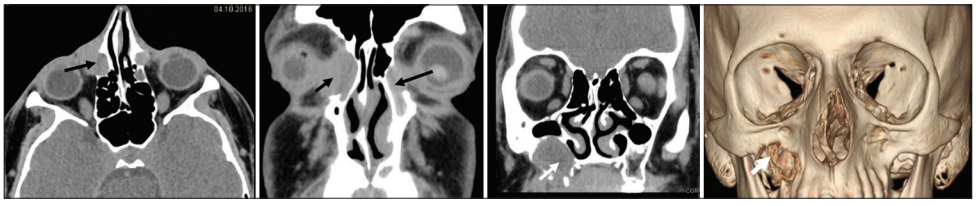

Figure 2: Axial computed tomography scan showing right cystic lesion, fluid-filled structure (black arrows). Bilateral dilatated nasolacrimal duct ending in bone obstruction. Lacrimal gland marked hypoplastic on the right side and hypoplastic on the left side. In the temporal bone, the middle ear ossicles were normal on both sides. Coronal and 3-D coronal surface shaded display fluid containing destructive expansible lesion originating from the alveolar process of the right maxilla (white arrow). Expansive lesion seen involving from the right maxilla is no longer seen after lacrimal cyst removal

detected in the clinical or in the imaging examinations impairs saliva production, which occur in 65.7% of LADD cases. A decrease in saliva leads to xerostomia and persistent dry mouth with swallowing problems and a greater susceptibility to serious dental erosion, periodontal disease, increasing risk of dental caries, and precocious loss of teeth.

The feature most strongly related to LADD is abnormal hands, feet, and limbs, present in 91.4% of the LADD carriers.[1-5,7-15,17-22,24-28] There are several distinct anomalies of distal limb and digit abnormalities, such as long phalanges, hypoplastic thumbs and radii, extra or missing fingers, curved pinky fingers, lateral or medial bending of the digits (clinodactyly), and webbing or fusion of the digits (syndactyly). Sometimes, it is possible to find shorter forearm with abnormal wrist and elbow joint development that limits movement.

Our patient did not have renal abnormalities. However, many different kinds of renal anomalies as nephrosclerosis, hydronephrosis, recurrent urinary tract infections, and other genitourinary system abnormalities were described in 69.7% of LADD cases.[2,5,6,10-12,17,20]

All the LADD alterations detected in the lacrimal and salivary glands, ears, skeleton, and many other organs can be the result of abnormal genes as *FGFR2*, *FGFR3*, and *FGF10*, which can stimulate cells to form structures for these affected organs. Mutations in these genes can result in impairment in cell maturation and development of many tissues, leading to the signs and symptoms of LADD syndrome.[24]

There are no standard guidelines for managing LADD. Treatment approach needs to be customized to the patient complaints. We removed the large dacryocystocele, and no further procedures were warranted since epiphora was not present. If epiphora is present, external/endonasal dacryocystorhinostomy associated to opening of the upper lacrimal excretory lacrimal system or Jones tube can be useful. If the dacryocystocele is not too large, it is not necessary to remove[31] as we did in the left side.

Conclusion

We present an adult patient with bilateral agenesis of the lacrimal puncta and canaliculi and large right lacrimal sac dacryocystocele. These features were detected in conjunction with auricular, dental and digital abnormalities, confirming the diagnosis of LADD syndrome. Our patient had an atypical mucocele in the maxillary sinus, which disappeared after dacryocystocele removal probably due to recovery of sinus drainage.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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