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CASE SERIES

Familial Occurrence of Isolated Late-onset Nasolacrimal Duct Obstruction in Two Unrelated Families

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ABSTRACT

Late-onset nasolacrimal duct obstruction (NLDO) as a result of inflammatory processes causing dacryostenosis is a common entity affecting mostly women. While a few mechanisms have been suggested as contributors to the expression of NLDO, the trigger for the inflammation remains mostly unknown. Familial predilection for this condition has not been previously reported. We present two families with multiple individuals affected with congenital or late-onset NLDO, describe the signs and symptoms of the affected individuals, and explore their medical history for any contributing factors. Family A, spanning four generations, included 7 female patients affected by late-onset NLDO. Family B, spanning two generations,

Abbreviations: CNLDO, congenital nasolacrimal duct obstruction; NLDO, nasolacrimal duct obstruction; PANDO, primary acquired nasolacrimal duct obstruction; SANDO, secondary acquired nasolacrimal duct obstruction.

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included 8 individuals affected by either congenital or late-onset NLDO. This case series suggests a familial predisposition to NLDO, apparently with an autosomal dominant inheritance pattern. Further studies are needed to elucidate the molecular basis of this genetic predisposition.

KEY WORDS: Endo-DCR, epiphora, nasolacrimal duct obstruction, oculoplastic

INTRODUCTION

Nasolacrimal duct obstruction (NLDO) is associated with epiphora and recurrent dacryocystitis and usually requires surgical intervention. The congenital form (CNLDO) is caused by incomplete perinatal perforation of the membrane present at the nasolacrimal duct opening. Late-onset disease is thought to be associated with obstruction along the nasolacrimal duct and is subdivided into primary and secondary acquired nasolacrimal duct obstruction (PANDO and SANDO, respectively).[1] Primary acquired NLDO is caused by inflammation and fibrosis of the nasolacrimal system without any known precipitating cause, although anatomical and hormonal predisposing factors have been suggested.[2–6] The smaller bony diameter of the lacrimal duct or reduced expression of estrogen receptors in lacrimal mucosa is more pronounced in women than in men, contributing to the higher incidence of PANDO in females. Of all the non-traumatic forms of dacryostenosis, PANDO accounts for most of the cases observed in adults. The secondary form is diagnosed when the patient's history indicates likely causes such as trauma, sinus disease, sinus surgery, or systemic diseases.[1] The exact incidence of late-onset NLDO is not known, although it is considered quite common.[7]

Familial occurrence of CNLDO has been reported previously. In most of these cases, CNLDO occurred as part of a systemic syndrome or was associated with various developmental anomalies. Little is known regarding the inheritance pattern of isolated CNLDO. Several studies have suggested familial occurrence of isolated CNLDO with an autosomal dominant pedigree pattern, but the genetic basis has not been identified.[8] Only one germline mutation associated with CNLDO has been reported to date. Foster et al. identified a homozygous IGSF3 mutation in a consanguineous family with CNLDO.[9]

To the best of our knowledge, there have been no reports of familial occurrence of late-onset NLDO. Here we report two large unrelated Israeli Jewish families of Moroccan and Ashkenazi ancestry with several members affected by isolated late-onset NLDO. In one of the families, both CNLDO and late-onset NLDO were found. We describe the clinical features of the disease in these two families.

THE CLINICAL CASE SERIES

Several patients from two unrelated families of Israeli Jewish ancestry presented to the oculoplastic clinic in the ophthalmology department at Soroka University Medical Center (SUMC), Beer-Sheva, Israel, with similar complaints of epiphora. Their pedigrees were obtained, and they underwent complete ophthalmic examination. General medical history was reviewed, and systemic symptoms and signs were recorded. Clinical data, including demographics, clinical presentation, systemic and ocular disorders, and treatment were collected for all affected individuals. The diagnosis of PANDO and CNLDO was made by history and physical examination, as well as by Jones tests, when needed. Study of this case series was approved by SUMC Institutional Review Board and Ethics Committee and adhered to the tenets of the Declaration of Helsinki.

Family A

Family A included 7 female patients with late-onset NLDO spanning four generations (Figure 1). This non-consanguineous family was of Moroccan Jewish ancestry. All females diagnosed with late-onset NLDO were daughters of mothers also affected by the condition. The age of onset ranged from 18 to 40 years, with the presenting sign in all cases being epiphora (Table 1). Most affected individuals had no history of chronic ocular or periocular inflammation, sinus inflammatory disease, or systemic abnormalities. Most affected individuals had normal findings on ophthalmic examination and no sinonasal pathology except NLDO. Blepharitis and cataract were diagnosed in two different subjects; however, these conditions are not known to be associated with NLDO. None of the patients had ptosis, facial dysmorphism, or abnormalities of eye movements. Two subjects had a history of sinusitis, but no correlation was found between sinusitis onset and epiphora exacerbations. Surgical intervention was necessary

for NLDO treatment in all but one patient. A computed tomography scan of the orbits in one patient revealed normal results, showing no pathological or contributing factors to the obstruction.

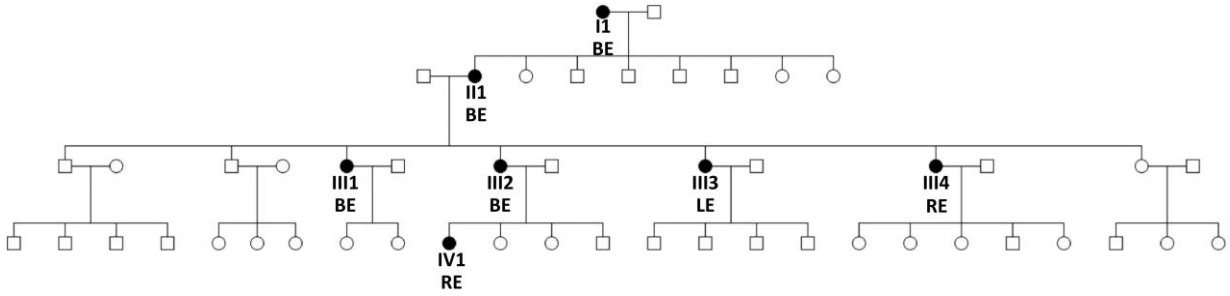

Figure 1. Family A Pedigree.

Squares represent males; circles represent females; black filled objects indicate individuals with late-onset nasolacrimal duct obstruction. Subject numbers correspond with those used in Table 1.

BE, both eyes; I, first generation; II, second generation; III, third generation; IV, fourth generation; LE, left eye; RE, right eye.

Table 1. Family A: Demographics and Medical History of Affected Individuals.

Parameter	Subject Number						
	I1	II1	III1	III2	III3	III4	IV1
Sex	F	F	F	F	F	F	F
Age at onset (years)	40	40	22	18	37	32	25
Eye involved	BE	BE	BE	BE	LE	RE	RE
Epiphora	Y	Y	Y	Y	Y	Y	Y
Dacryocystitis	N	N	N	Y	Y	Y	N
Other ocular conditions	N	N	N	Blepharitis	N	Cataract	N
Topical eye treatment	N	Tobramycin	N	N	N	N	N
Smoking	N	N	N	N	N	N	N
Other sinonasal disorders	N	Chronic rhinitis Acute sinusitis	N	N	N	N	Chronic sinusitis
Other systemic diseases	DM	N	N	N	N	N	N
Treatment	Conservative	RE: EXT-DCR LE: ENDO-DCR	LE: EXT-DCR RE: EXT-DCR RE: ENDO-DCR RE: ENDO-DCR*	RE: ENDO-DCR LE: EXT-DCR	LE: ENDO-DCR	RE: ENDO-DCR	RE: ENDO-DCR

BE, both eyes; DES, dry eye syndrome; DM, diabetes mellitus; ENDO-DCR, endoscopic dacryocystorhinostomy; EXT-DCR, external dacryocystorhinostomy; F, female; I, first generation; II, second generation; III, third generation; IV, fourth generation; LE, left eye; M, male; N, no; RE, right eye; Y, yes.

*Repeat procedure at different times after failure and return of epiphora.

Family B

Family B, of non-consanguineous Ashkenazi ancestry, included 8 affected individuals: 2 female patients in generation II were affected by late-onset NLDO, 1 patient in generation II was affected by CNLDO, and 2 male and 3 female patients in generation III were affected by CNLDO which spontaneously resolved with age (Figure 2). No predisposing factors to NLDO were noted (Table 2). Among the CNLDO cases, two were confirmed and recorded by a physician, and the other four were reported by parents.

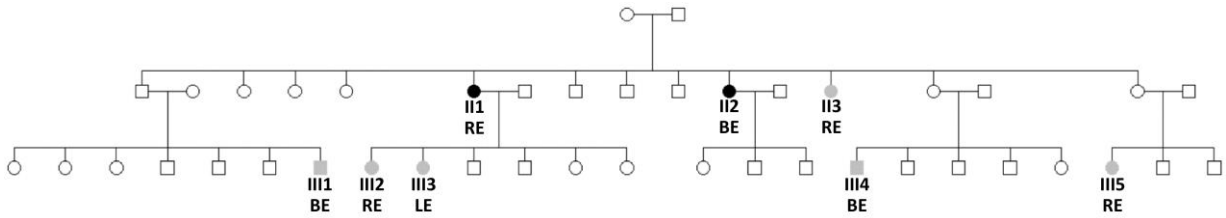

Figure 2. Family B Pedigree.

Squares represent males; circles represent females; black filled objects indicate individuals with late-onset nasolacrimal duct obstruction; gray filled objects indicate individuals with congenital nasolacrimal duct obstruction. Subject numbers correspond with those used in Table 2.

BE, both eyes; II, second generation; III, third generation; LE, left eye; RE, right eye.

Table 2. Family B: Demographics and Medical History of Affected Individuals.

Parameter	Subject Number							
	II1	II2	II3	III1*	III2*	III3*	III4*	III5
Sex	F	F	F	M	F	F	M	F
Age at onset	36 yr	16 yr	5 yr	6 mo	6 mo	1 yr	6 mo	4 yr
Eye involved	RE	BE	RE	BE	RE	LE	BE	RE
Epiphora	Y	Y	Y	Y	Y	Y	Y	Y
Dacryocystitis	N	Y	N	N	N	N	N	N
Other ocular conditions	N	N	N	N	N	N	N	N
Topical eye treatment	Ofloxacin Dexamethasone	Ofloxacin Dexamethasone	N	N	N	N	N	N
Smoking	N	N	N	N	N	N	N	N
Other sinonasal disorders	N	N	N	N	N	N	N	N
Other systemic diseases	N	N	N	N	N	N	N	N
Treatment	LE: ENDO-DCR	LE: ENDO-DCR	Conservative	N	N	N	N	N
Comments	N	N	Down syndrome, CNLDO	Epiphora, CNLDO*	Epiphora, CNLDO*	Epiphora, CNLDO*	Epiphora, CNLDO*	Epiphora, CNLDO

BE, both eyes; CNLDO, congenital nasolacrimal duct obstruction; DES, dry eye syndrome; DM, diabetes mellitus; ENDO-DCR, endoscopic dacryocystorhinostomy; F, female; II, second generation; III, third generation; LE, left eye; M, male; mo, month; N, no; RE, right eye; Y, yes; yr, year.

*Reported by parents, spontaneous resolution noted with age.

DISCUSSION

We report two unrelated extended families with multiple members affected by late-onset NLDO. The absence of associated systemic conditions or local risk factors for NLDO implies a genetic predisposetion. While familial cases of CNLDO have been traced, to the best of our knowledge, this is the first report of familial occurrence of late onset NLDO.

The incidence of PANDO is greater in women than in men.[1] This higher occurrence in females is thought to be the outcome of significantly smaller dimensions of the lower nasolacrimal fossa and middle nasolacrimal duct. Groessl and colleagues noted that changes in the anteroposterior dimensions of the bony nasolacrimal canal coincide with osteoporotic changes throughout the body.[2] Others have suggested menstrual and hormonal fluctuations and augmented immune status as factors that may contribute to the disease process.[3–6] These may explain the high prevalence of PANDO in middle-aged and elderly women, when the hormonal changes leading to generalized de-epithelialization in the body may cause the same process within the lacrimal sac and duct.[1] It is possible that an anomalous nasolaryngeal duct structure is inherited in an autosomal dominant fashion in both sexes, but the already narrow lacrimal fossa in women predisposes them to obstruction by sloughed-off debris, thereby manifesting as overt NLDO only in affected females. The fact that only female family members in Family A were affected with NLDO could also imply a non-Mendelian mode of inheritance. In Family B, however, two male children were affected by CNLDO. Moreover, three CNLDO patients had mothers with no history of NLDO. Therefore, if late-onset NLDO and CNLDO are considered as the same entity, the most likely mode of heredity is autosomal dominant with incomplete penetrance and variable expression.

The occurrence of both late-onset NLDO and CNLDO in Family B could imply that late-onset NLDO might be a form of occult CNLDO that becomes clinically apparent after puberty. Affected individuals in Family B developed a more severe, congenital disease in the younger generation as opposed to the milder, adult-onset disease in older individuals, which may indicate the mechanism of genetic anticipation. It should be mentioned that while a few studies suggested familial occurrence of congenital dacryocystocele and CNLDO, a clear inheritance pattern has not been reported, except for the association with a homozygous IGSF3 variation in one consanguineous family with CNLDO.[9]

In summary, to the best of our knowledge, this is the first report of familial occurrence in two unrelated non-consanguineous families of late-onset NLDO, with likely autosomal dominant heredity with incomplete penetrance and variable expression. Further studies are needed to elucidate the molecular basis of this genetic predisposition.

REFERENCES

1. Worak SR, Bengzon AU. Nasolacrimal duct obstruction and epiphora. Updated June 16, 2023. Medscape. Available at: https://emedicine.medscape.com/article/1210141-overview (accessed December 6, 2023).
2. Groessl SA, Sires BS, Lemke BN. An anatomical basis for primary acquired nasolacrimal duct obstruction. Arch Ophthalmol 1997;115:71–4. CrossRef
3. Ali MJ, Schicht M, Paulsen F. Qualitative hormonal profiling of the lacrimal drainage system: potential insights into the etiopathogenesis of primary acquired nasolacrimal duct obstruction. Ophthalmic Plast Reconstr Surg 2017;33:381–8. CrossRef
4. Ohtomo K, Ueta T, Toyama T, Nagahara M. Predisposing factors for primary acquired nasolacrimal duct obstruction. Graefes Arch Clin Exp Ophthalmol 2013; 251:1835–9. CrossRef
5. Taban M, Jarullazada I, Mancini R, Hwang C, Goldberg RA. Facial asymmetry and nasal septal deviation in acquired nasolacrimal duct obstruction. Orbit 2011;30:226–9. CrossRef
6. Kashkouli MB, Sadeghipour A, Kaghazkanani R, Bayat A, Pakdel F, Aghai GH. Pathogenesis of primary acquired nasolacrimal duct obstruction. Orbit 2010;29:11–15. CrossRef
7. Woog JJ. The incidence of symptomatic acquired lacrimal outflow obstruction among residents of Olmsted County, Minnesota, 1976–2000 (an American Ophthalmological Society thesis). Trans Am Ophthalmol Soc 2007;105:649–66. PMCID: PMC2258133
8. Suh DW, Haklmeh C, Shahraki K. Congenital anomalies of the nasolacrimal duct. Updated December 1, 2023. Medscape. Available at: https://emedicine.medscape.com/article/1210252-overview (accessed December 6, 2023).
9. Foster J 2nd, Kapoor S, Diaz-Hortaa O, et al. Identification of an IGSF3 mutation in a family with congenital nasolacrimal duct obstruction. Clin Genet 2014;86:589–59. CrossRef