

# BILATERAL AMYLOIDOSIS OF THREE EYELIDS - REVIEW

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Dedicated to the memory of the famous European ophthalmic histologist, Prof. František Vrabec, MD, PhD, 110 years having passed since his birth.

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## SUMMARY

**Aim:** To present rare form of lids amyloidosis, in the context with literature and remind a Czech professor Vrabec, F., MD, an important pan-European ocular histologist.

**Case report:** A 37-year-old male was examined for eyelids' mass at the Department of Ophthalmology of Kralovske Vinohrady Teaching Hospital in Prague, the Czech Republic in June 2018. The finding appeared like chronic chalazion on the right side and chronic hordeolum on the left side. No acute phase had been noted by the patient within the past few months. A yellowish to lightly brown friable, partially transparent mass was obtained by excision. Amyloidosis of the AL type was revealed histologically, and diagnosis was followed by extended excision and plastic surgical reconstruction of the lower eyelids on both sides. In April 2021, a similar process was verified on the upper right eyelid with a 3-month clinical history. No systemic disease underlying the amyloidosis was disclosed by following through a diagnostic work-up of the patient in both periods.

**Results:** Amyloidosis was illustrated initially by Congo red staining with characteristic dichroism in the polarised light. It was then analysed immunohistochemically, with positivity for Kappa light chains. Systemic amyloidosis was excluded, as well as monoclonal gammopathy. Only a slightly increased number of plasmacytes (up to 10%) was revealed in the bone marrow biopsy. The surgical solution was optimal for the patient, and he suffered no recurrence or problems of the lower eyelids for 3 years.

**Conclusion:** The described case of bilateral eyelid amyloidosis without underlying systemic disease belongs among the rare cases and also illustrates the necessity of complex interdisciplinary collaboration in the diagnostic process and long-term monitoring.

**Key words:** ocular amyloidosis, palpebral mass, plastic surgery of conjunctiva

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## INTRODUCTION

The first extensive analysis of the ocular issue of amyloidosis can be found in an extensive 15<sup>th</sup> volume monograph by Sir Sterward Duke-Elder [1], which provides a breakdown of publica-tions from the 1960s, when the ocular symptomatology of this clinical unit was defined. Amy-loidosis has already been divided into primary and secondary forms. The main localisations of the primary

disorder were the muscles and nerves, the cardiovascular system and the skin. It was the skin of the eyelids that formed the frequent localisation for amyloid deposits (Figure 1, left), while the conjunctiva was the second possibility of ocular symptomatology, given the di-agnostic events of the time. The secondary form was considered in connection with chronic inflammation, such as tuberculosis, syphilis, or rheumatoid arthritis, as well as with metabolic diseases (diabetes mellitus and dysproteinaemia). Among eye

diseases, secondary infiltration occurred in trachoma. Multiple causes of amyloid formation have been considered, namely production from the reticuloendothelial system or plasmacytes or fibroblasts. An association between hyaline and amyloid was sought in terms of hyaline degeneration. Amyloid was defined with a fairly stable chemical entity of the complex of glycoprotein and neutral mucosaccharides, histologically detectable by methyl or essential violet or Congo red, its dichroism was already known.

Professor František Vrabec, MD, PhD (Figure 1, right) contributed a total of 130 original histological images to this unique encyclopaedia. These were mainly photomicrographs of findings of nerve endings in the iris-ventricular angle, pathological innervation of the cornea, neurohistology of retinal pigment degeneration, together with other observations. More than half of these images were taken from the important 13 volumes of the German eye textbooks, *Der Augenzart* (Velhagen, K. Editor, 1969, VED Georg Thieme, Leipzig). Professor Vrabec introduced new histological procedures: e.g. silver preparation and the method of replication. This resulted in more than 200 original works. After graduating in 1939, he began his professional career at the Czech Eye Clinic in Prague. During World War II, he was transferred to the Eye Department of Vinohrady Hospital, but returned to the Czech Eye Clinic after the War. Here, in 1954, he received his doctoral degree and, in 1959, won the competition for the vacant position of Head of the Eye Clinic of the Faculty of Hygiene in Vinohrady, after its first Head, Professor Josef Janků. He completed several internships at prestigious workplaces, then behind the Iron Curtain. He was elected a member of the European Ophthalmic Pathology Society, of which the Czech Republic is a member to date. He was awarded full Professorship in 1966 and was Head of the Eye Clinic until 1976 [2]. Even after retirement, he continued to work in his histological laboratory at the Hospital and at the Institute of Experimental Medicine of the Czechoslovak Academy of Sciences. Through his activities, he helped many young colleagues to produce quality publications. With his last co-authorships in Czechoslovak Ophthalmology, he supported the

priority observation of ocular manifestations of oxalose on the retina, in the form of brightly glowing crystals in polarising light under the retinal pigment epithelium [3], and the presence of congenital posterior cortical cataract with convex-concave lens shape in Pierre-Robin syndrome [4]. Professor Vrabec was one of the most important personalities in Czechoslovak Medicine in the second half of the last century and also established himself in European Ophthalmology with his histological studies.

Amyloidosis is currently considered a multiorgan disease, caused by amyloid deposits of various protein compositions. Amyloid is formed by fibrils of the parent protein, based on its crystallisation-like process and on clusters of pathological protein precursors. It can be localised in a number of organs, whether primary light chain amyloidosis (AL amyloidosis) or secondary amyloidosis accompanying chronic inflammation (AA amyloidosis), locally or systemically.

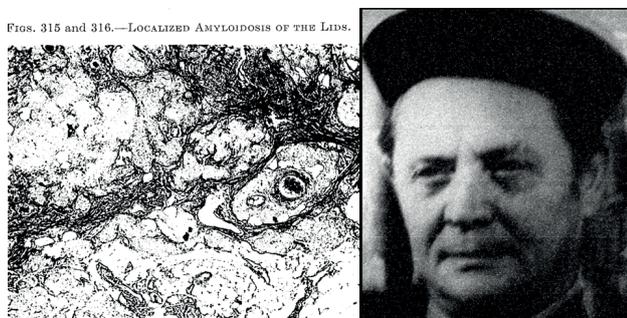
Single-organ involvement includes the brain in Alzheimer's disease or the Islets of Langerhans in the pancreas in diabetes. Systemic primary disease is most commonly manifested in the kidney, where amyloid is deposited in the loops of the glomeruli, later in the interstitium, and can lead to their failure. In the spleen, amyloid is deposited in both the red and white pulps and then creates a macroscopic image of the so-called sago or ham spleen. In the intestine, it affects the mucous and submucosal trees and the walls of small blood vessels and leads to malabsorption syndrome. Its deposition in the myocardium causes fibrillation in the atria of the heart and leads to fatal heart failure in the ventricular myocardium. It may also be related to polyneuropathy in peripheral nerve disorders. The secondary form represents a disability in chronic inflammation; this is currently mainly rheumatoid arthritis [5,6].

Previously observed observations from the 1960s of conjunctival involvement of the complex of the eyelids with conjunctiva have been expanded to confirm further localisations of amyloidosis in the orbit, vitreous and cornea, and secondary glaucoma has been reported.

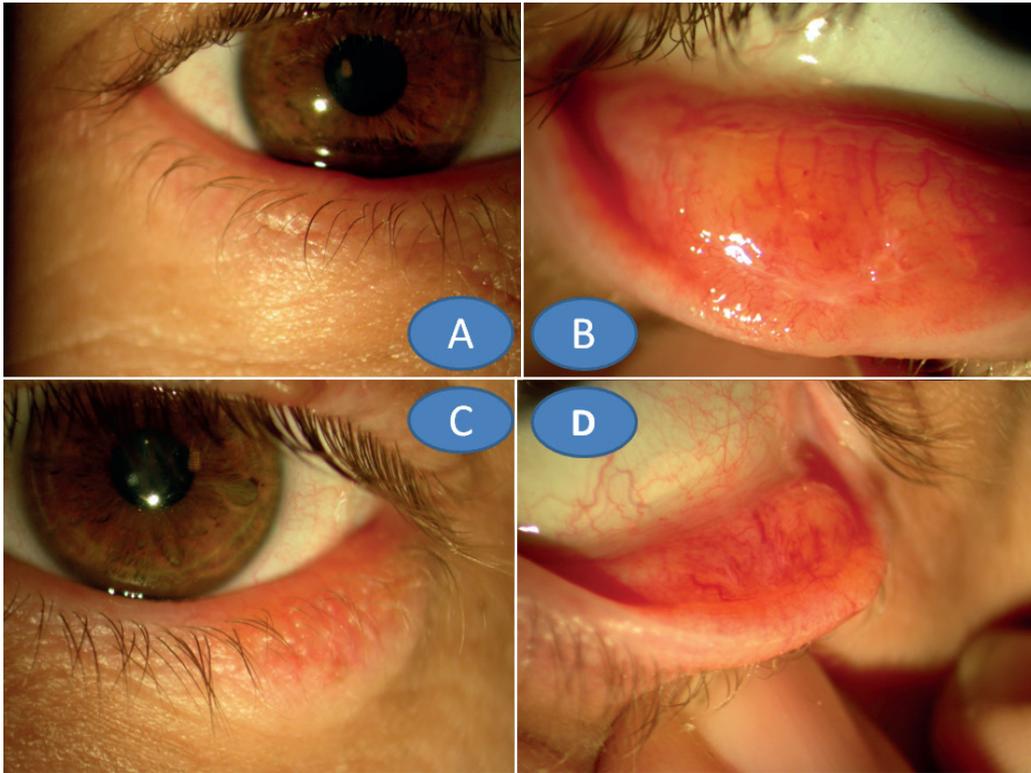
## CASE STUDY

A 37-year-old patient arrived at the beginning of June 2018 at the Outpatient Clinic of the Department of Ophthalmology of Královské Vinohrady Teaching Hospital in Prague (Czech Republic) with a six-month history of eyelid inflammation under the clinical picture of chronic chalasia on the right: spherical arch of the lower eyelid without inflammatory alteration with redness (Figure 2 – A, B) and chronic lower eyelid hordeola: sector-like redness of the margin from the eyelid side turned into a solid sector on the tarsal side

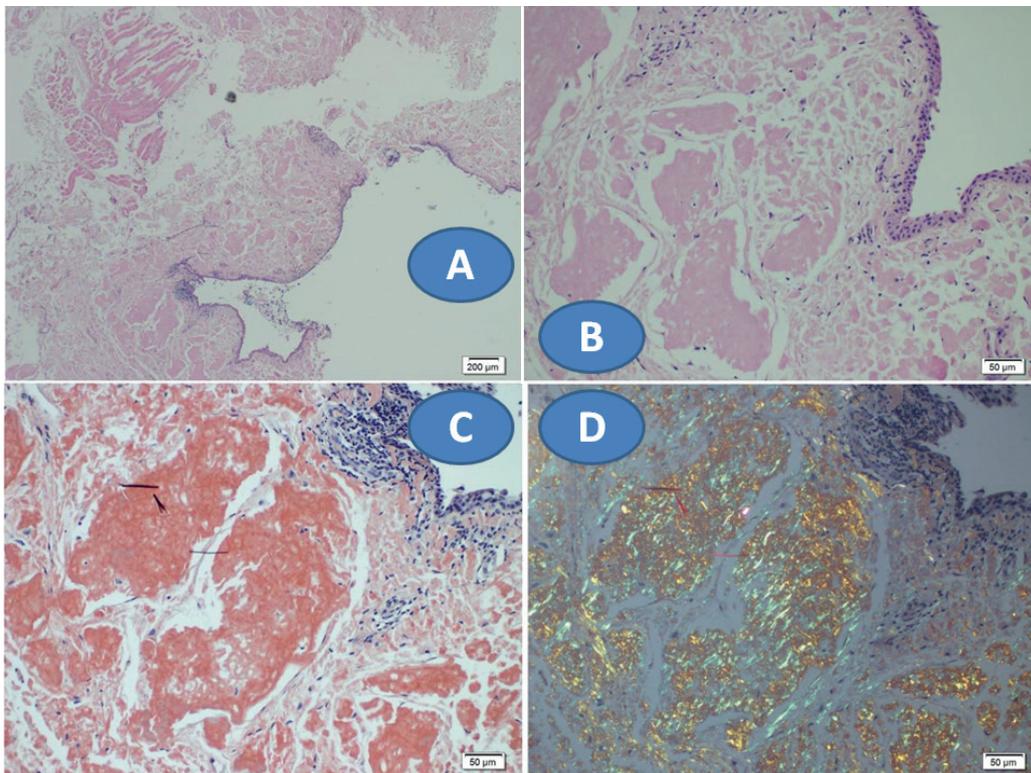
(Figure 2 – C, D). Anamnestically, the patient did not report the acute phase of the two diseases. Surgical treatment was started at the end of that month. Under local anaesthesia, the process was excocleated on the right and excised on the left. Due to the atypical natu-



**Figure 1. Left** – Deposits of amyloid of the lid (took over Duke-Elder, S.: *System of Ophthalmology*, Kimpton, 1974, Vol. XIII. p. 313) **Right** – Prof. František Vrabec MD, PhD (1911–2000)



**Figure 2.** Lesion of the lower right eyelid, appearance of chronic chalazion. Lesion of the lower right eyelid, appearance of chronic chalazion (A, B). Lesion of the left lower eyelid, appearance of chronic hordeolum (C, D)



**Figure 3.** Deposits of amyloid – Eosinophil mass within the lid, HE, 40x (A) and 200x (B), positive Congo red, 200x (C), Congo red, polarised light, 200x (D)

re of the material collected on the right, which was beige-yellowish, translucent and friable, not dirty yellow, opaque and compact as in chalazion, the material was sent for histological examination to rule out a malignant process. These revealed deposits of eosinophilic mass, demonstrating the properties of amyloid AL (Figure 3 – A, B). Due to the persistence of resistances in both lower eyelids, in November of the same year, they were removed under general anaesthesia, using the conjunctival approach, after which the tarsal conjunctiva was performed. The resistances were 12x7x7 mm and 13x8x5 mm.

Histology: AL-type amyloid was again confirmed in the conjunctival stroma (consisting of immunoglobulin light chains), first in Congo red staining (with and without permanganate oxidation), which was characterised by a brick-red staining (Figure 3C), with the presence of dichroism during this colouring in polarised light: alternation of yellowish and greenish colouration (Figure 3D). Amyloid deposits were also seen in the walls of some small vessels. No tumour structures or actual inflammatory changes were found. The basic examination was supplemented by immunohistochemical examination. The presence of Kappa light chains and, to a lesser extent, Lambda was confirmed (Figure 4 – A, B) in amyloid deposits and sites in vascular walls. The detection of SAA protein (which would be characteristic of chronic general inflammation) and transthyretin (another possible precursor of amyloid) was negative in amyloid deposits.

Overall comprehensive examination (confirmed the above reasoning):

a) normocellular bone marrow with trilinear haemopoiesis present, more frequent CD138 plasma cells (brown stained), but did not exceed 10 % of total cellularity (Figure 4 – C, D)

b) Amyloid was not detected in the rectal mucosal sample

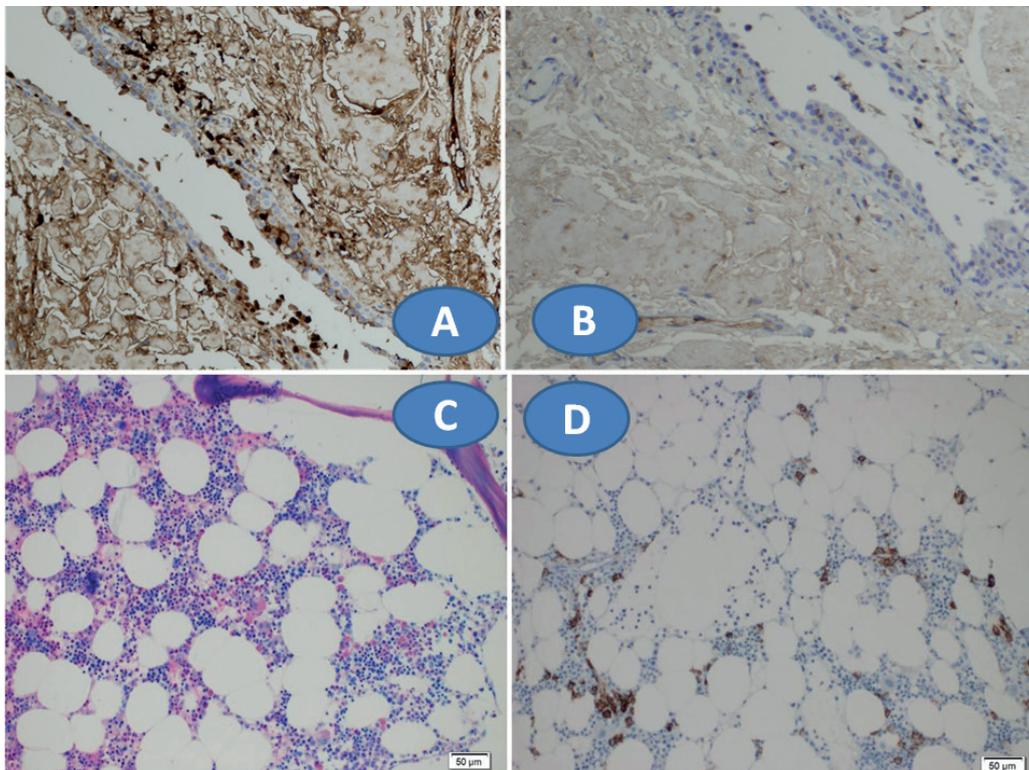
c) Monoclonal gammopathy was not confirmed for both Kappa chains and Lambda chains

d) Physiological level of free Kappa chains (using the FLC kit) did not indicate a systemic form of the disease

**Summary:** This was therefore a localised form of AL amyloidosis, without evidence of multiple myeloma or other blood diseases.

In December 2020, the eyelids were without recurrence, the tarsal conjunctiva was normally contoured (Figure 5AB on the right and Figure 5CD on the left) and the overall condition was free of systemic manifestations. The patient was included in the ocular and haematological internal dispensary.

**Note:** In April 2021, another deposit of amyloidosis, again under the image of chalazion on the upper left lid was histologically verified. At that time, both lower eyelids did not show a pathological process. The overall examination was again negative.



**Figure 4.** Immunohistochemistry – Kappa light chains (A) and Lambda light chains (B), bone marrow trephine biopsy, Giemsa, 200x (C) and CD138 (marker of plasma cells) 200x (D)



**Figure 5.** Normal condition of the lower eyelids two years after total resection and plastic surgery: right side (A, B) and left side (C, D)

## DISCUSSION

Amyloidosis is currently divided into more than 20 separate diseases. There are also congenital types and acquired types, some of which are locally bound (e.g. Finnish hereditary amyloidosis or British familiar dementia). AL amyloidosis, as in our patient, is caused by an acquired mutation and overproduction of amyloid, formed by immunoglobulin light chains based on plasma cell proliferation. It is also called primary amyloidosis, the incidence of which in Western countries is 1:100 000 new cases per year. [5,6].

The first large-scale study of five patients confirming three orbital amyloidosis, two-sided lacrimal gland involvement and twice their own orbital infiltration, appeared in the 1970s. The other two patients had conjunctival involvement, and no systemic involvement was confirmed in the cohort [7]. A retrospective evaluation of two studies from this century of AL amyloidosis with orbital symptoms, including auxiliary organs [8,9] revealed systemic involvement in only one case out of a total of 106 patients. Both studies showed almost two-fold disabilities in women: 54:28 [8] or 15:9 [9] and a similar mean age of 54.9 (18–87 years) [8] or  $57 \pm 17$  years [9]. The last study from 2018 included only four members, the age representation was similar to  $52 \pm 9.4$  years, with a predominance of three females. These were unilateral lesions in the area of the tarsal conjunctiva, lacrimal gland, orbit, which

was accompanied by ptosis, and the lacrimal sac. The calcification demonstrated in the three biopsy specimens increased the suspicion of amyloidosis.

Only the orbital form has been shown to have systemic involvement [10]. Unilateral disability predominated in 80% [9], as a second study of 14 unilateral self-observations included additional observations from literature data [8]. The clinical symptoms in the total sum of both studies included mainly eyelid infiltration in 4/5 cases, accompanied by ptosis in 1/3 of cases. The protrusion of bulbs in 1/5 of patients was also limited by the eye motility disorder in every other person affected in this way [8,9]. After verification of the process, two procedures are recommended, non-intervention or total extirpation, which rather guarantees the cessation of the process, and which can be repeated in the advanced form of eyelid amyloidosis [11]. We chose this procedure ourselves. To date, the situation has stabilised. Complete excision in the orbital form is not possible in many cases [9]. However, in 2/3 the finding stabilised after diagnostic excision, and in 1/3 recurrence occurred, with the need for further surgery [8]. Excision has always reduced the exophthalmos [12].

Ocular manifestations in systemic AL amyloidosis are rare; in one of the most numerous studies in the last three years, ocular involvement was reported in 68 patients in only 8 (12%) patients with 14 eyes, mainly in the conjunctiva, extraocular muscles or with secondary glaucoma. [13]. Systemic involvement was diagnosed

by rectal biopsy in a 67-year-old patient with atypical, acquired exotropia and hypertropia, when strabismus progressed. MR revealed muscle swelling, lacrimal gland involvement was ruled out, and a biopsy of the muscles revealed amyloid deposition [14]. In AL amyloidosis, systemic involvement should be ruled out, although it is rare. We also performed a comprehensive examination of our patient. There was less than 10% of plasma cells in the bone marrow, which ruled out manifest multiple myeloma [5,6]. Apart from the histological findings in the eyelids, we did not show an overproduction of light chains in general, which confirmed the absence of systemic involvement, as no free chains appeared in such an amount as to cause amyloid deposits in another location [5,6].

Amyloidosis of the lower eyelids is less common than the upper eyelids, due to the tarsal involvement in this location, with bilateral eyelid involvement being rare. We did not find a report on the involvement of three eyelids in the literature. We believe that this was not a recurrence of the basic process, but an additional development of hidden bearing deposit on the upper lid with an interval of three years. Chalazion appeared in the differential diagnosis as early as the 1960s [1], which was also in our balance sheet. We performed histological verification to rule out malignancy such as Merkel's carcinoma, which also includes chalazion in the differential diagnosis [15], not to suspect amyloidosis. A similar macroscopic description of the character of the tissue obtained during the operation, as in our case, was previously defined in our region as a yellow-brown, gelatinous, and easily crumbling mass [16].

Separate conjunctival involvement was observed in the early diagnosis of ocular amyloidosis [1], and is characterised by yellow-pink [17,18] or salmon-pink [19] infiltrates, which may be combined with deep-seated haemorrhages [18,20,21]. Anamnestically, the long-term onset of symptoms with a course of disability lasting from five years [21] to even ten years [20], unresponsive to local antibiotic treatment, is characteristic. It is always necessary to exclude the malignant process for which biopsy is used [17,19,20,21]. Depending on the location of the process, it may trigger epiphora in tear duct stenosis [22] and ectropion of the lower eyelids [17]. Unilateral conjunctival involvement of both eyelids has already been reported in a 19-year-old male [23]. Amyloid infiltrations tend to be in the bulbar conjunctiva and possibly also in the fornix area [18,19,21], in the tarsal conjunctiva [17,21] of the lower eyelid, but also in the semilunar lung [24]. Significant and extensive involvement of the upper tarsal conjunctiva can cause ptosis [1,23,24,25]; the differential

diagnosis in this localisation also includes vernal catarrh [26]. Therapeutically, excision is recommended [18,19,23] possibly supplemented with cryotherapy [20,23] and topical corticosteroids to alleviate the symptoms of chemosis [20,21]. Tear duct stenosis [22] and ectropium [17] have been successfully treated surgically. Surgical management of ptosis in younger patients aged 23 years [26] and 31 years [25] was cosmetically and functionally successful, even after five years in a single bilateral form. Another four bilateral lesions have been reported in eyelid ectropia [1], lacrimal duct stenosis [21] and twice in bulbar conjunctivae in the lower fornixes [20,21] out of a total of 19 patients from the 11 studies from 2002 to 2018. Systemic involvement was confirmed in only 2 patients (10%), namely infiltration of the semilunar lung [24] and bilateral conjunctival [21].

Another localisation of amyloid deposition in the eye is associated with familial amyloid neuropathy with the transthyretin cys-114 mutation (TTR amyloidosis). Amyloid particles have been detected in the aqueous humour of secondary glaucoma, theoretically involving outflow obstruction as the mechanism of its formation [28]. This mutation was found in the bilateral intraocular process of vitritis with bleeding and retinal vasculitis in five Indians, one of which was accompanied by bilateral secondary glaucoma in ocular symptoms [29]. A detailed examination of 54 patients with TTR amyloidosis always revealed bilateral ocular involvement in 24% of them, with a predominance of females. In all patients, the vitreous was affected, causing a decrease in vision to an average of 0.2 and secondary glaucoma was 19%. It was caused 1 time by central venous occlusion, caused by intraocular amyloidosis [30]. With non-transthyretin familial amyloidosis, gelsolin-mediated corneal dystrophy was detected in 1 of the 5 patients [13]. Secondly, amyloid can appear in corneal tissue due to corneal damage during surgery, including treatment of its injury [31] or long-term wearing of hard contact lenses in keratoconus [32].

## CONCLUSION

We present a case report of bilateral eyelid amyloidosis in two periods, without the basis of systemic disease in a now 40-year-old patient. This is a sporadically occurring disease. The case documents the need for complexity of examination in interdisciplinary collaboration, to determine the extent of disability. Our report is the first mentioned information about ocular amyloidosis in the journal, Czech and Slovak Ophthalmology. In addition, this is a rare case study due to the localisation on three of the four eyelids.

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