LIGNEOUS CONJUNCTIVITIS AS A MANIFESTATION OF PLASMINOGEN DEFICIENCY: A REPORT OF TWO CASES WITH LONG FOLLOW-UP PERIODS

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Background

Plasminogen Deficiency (PLGD) is a chronic lifelong disease that starts in early childhood when it is most severe and persists for life, negatively affecting patient's health and quality of life.

PLGD is a rare autosomal recessive condition with a prevalence of 1.6 per 1 million of the population.

Severe PLGD results from homozygous or compound heterozygous mutations of the PLG gene on Chromosome 6q26-27 and leads to inadequate plasminogen levels and defective fibrinolysis.

Excessive buildup of fibrin in the eyes causes the rare but potentially blinding Ligneous Conjunctivitis (LC), which is the most common manifestation of severe PLGD, affecting 81% of patients. LC is characterized by chronic and recurrent episodes of pseudomembranous and membranous conjunctivitis leading to marked thickening of the upper and lower tarsal conjunctiva.

Extra-ocular manifestations of PLGD have been reported in approximately 12% of patients with LC. Systemic manifestations described include fibrin deposits involving different mucous membranes of the body such as the gingiva, larynx, respiratory tract, cervix and vagina. Obstructive hydrocephalus is the most serious manifestations in PLGD and occurs in up to 12% of patients.

Management & Treatment

Treatment of LC is notoriously difficult with no permanent cure. Surgical removal of membranes provides only short term (days) relief and potentially worsens and increase relapses.

Many treatments with variable success have been tried including topical heparin, cyclosporine A (CSA), a-chymotrypsin, hyaluronidase, mitomycin C, topical and systemic fresh frozen plasma (FFP), amniotic membrane grafting and systemic immunosuppression using corticosteroids and azathioprine. Heparin demonstrated efficacy when used following surgical membrane removal and this is thought to be due to its anti-fibrinolytic properties.

Topical plasminogen is the ultimate treatment for this disease, unfortunately its usefulness is hindered by cost and commercial unavailability. Concerns about sterility impedes its use when available. Lately, Plasminogen eye drops have been commercially formulated by one Pharmaceutical company.

Currently the most feasible way to administer plasminogen is utilizing topical ± systemic FFP, which is not always readily available to meet the frequent administration necessary to achieve disease control.

Despite all treatment options attempted, outcomes remain unsatisfactory with reports claiming 40% of patients experiencing recurrent disease with another 10% showing no response to treatment.

Case 1

A 7-month-old child born to consanguineous parents was referred to our Ophthalmology clinic with persistent eye swelling for 4 months resulting in difficulty opening both eyes. He was diagnosed with congenital hydrocephalus and underwent a VP shunt at the referring hospital that got blocked within 2 months and replaced by a VA shunt.

At presentation both eyes were almost completely occluded by the swelling. Both upper and lower palpebral conjunctival surfaces showed hard whitish gray membranes causing marked thickening of the eyelids and were associated with a large amount of thick purulent discharge. Based on the clinical findings he was suspected to have PLGD. Multiple specialties were involved for optimal management including Ophthalmology, Pediatric Hematology, Pediatric Neurosurgery and Interventional Radiology.

He was first treated for bacterial conjunctivitis with topical antibiotics followed by early institution of CSA 1% Q6H and fluoromethalone 0.1% Q6H. The diagnosis was confirmed by demonstrating plasminogen activity was 17% (normal range 75-140%), subsequently he was started on IV FFP 10ml/kg every day for 3 days followed by 10ml/kg every other day. Preservative free heparin eye drops Q4H were prepared in the pharmacy (5000 u/ml) and added to his treatments.

Surgical membrane peeling was performed to aid with eye opening as amblyopia was a primary concern. He continued both systemic & topical treatments as an inpatient and a new VP shunt was placed. Once his condition was stable he was discharged home on topical eye drops of CSA 1%, heparin 5000 u/ml and he continued to receive IV FFP every other day, with no recurrence of his membranes being noted to date.

Case 2

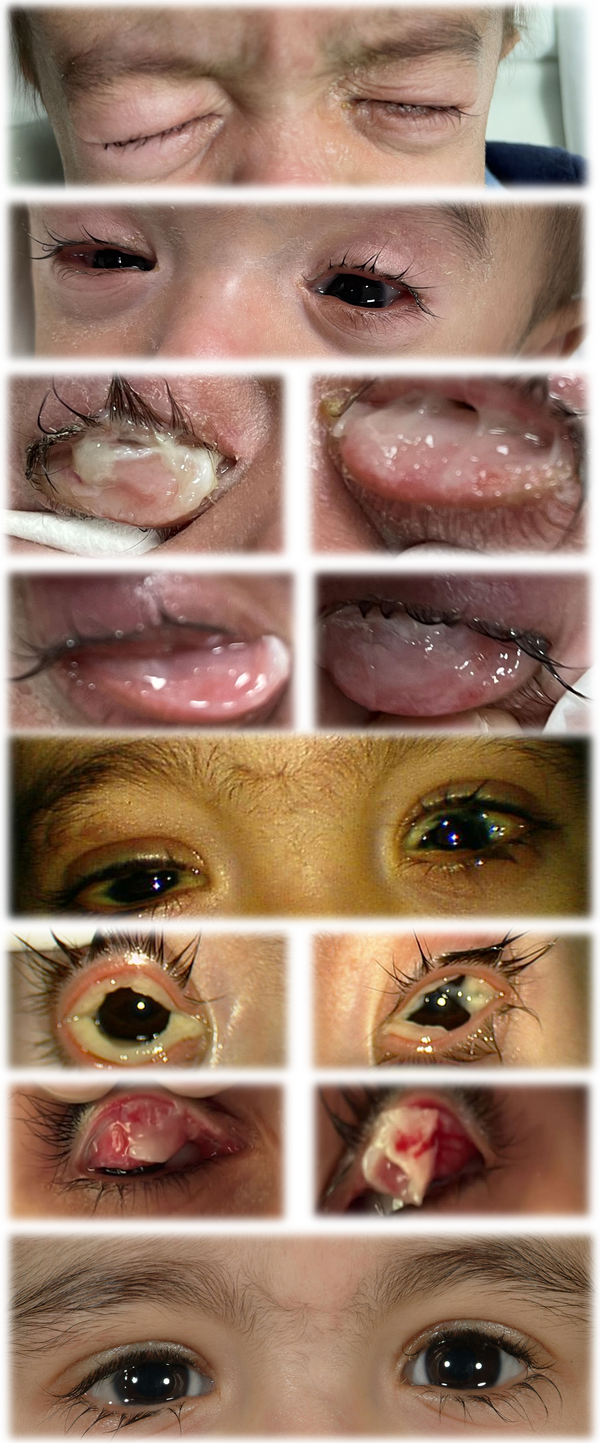
A 2-month-old girl presented with bilateral eye redness since birth that had been unresponsive to treatments associated with increasing head circumference. A workup for obstructive hydrocephalus was initiated as well as a referral to Ophthalmology.

Ocular exam showed bilateral external fullness to both eyes with whitish-yellow woody membranes on both the upper and lower palpebral conjunctiva. Consequently, a diagnosis of PLGD and LC was confirmed. She underwent surgical membrane peelings during the same admission to facilitate spontaneous eye opening and to avoid amblyopia as well as to facilitate topical therapy.

Topical FFP Q2H, CSA 1% Q8H and a short course of prednisolone acetate 1% with tapering dose were used topically in both eyes following surgical membrane peeling to prevent recurrence. IV FFP was added as per the Pediatric Heamatology recommendation. Later during her admission, she underwent a VP shunting procedure and was discharged on topical Plasminogen eye drops that were prepared by the local pharmacy Q4H, CSA 1% eye drops Q3H, lubrication 3 to 4 times weekly as an outpatient and IV Plasminogen as per the recommended dose.

Over the ensuing 6 months her ocular condition had improved dramatically, however, she required revision of her VP shunt due to occlusion, With continued systemic and local Plasminogen and other topical treatments the child reached satisfactory levels of circulating plasminogen and both her ocular and systemic condition improved.

Consequently, topical Plasminogen was decreased to Q6H and systemic Plasminogen to 2-3 times weekly. Eighteen years later the patient still has good control with relatively mild, occasional recurrences documented in periods of non-compliance, which respond to temporarily higher doses of topical and/or systemic Plasminogen.



Plasminogen Drop Formulation

Plasma (1U) is passed over a 100-ml Lysine-Sepharose column previously equilibrated in 0.1 mol/NaPi pH 8.0. It is washed with NaPi pH 8.0 until absorbance at 280 nm of collected fractions is below 0.01. The plasminogen is eluted with 20 mmol/l Epsilon aminocaproic acid in 20 mmol/l Tris pH 8.0. Peak fractions of plasminogen are pooled and precipitated with 75% ammonium sulfate. Following centrifugation, the supernatant is decanted and remaining pellet is dissolved in a minimum amount of 0.1 mol/l NaCl in sterile water and dialyzed exhaustively against the same (4x4 liters overnight at 4°C). Retained material is then subjected to filtrations using 0.45 μ filter attached to 30ml syringe into sterile tubes. Absorbance is determined using an extinction coefficient of 1.61 ml/mg/cm and the plasminogen is diluted to a concentration of 10uM (approximately 1mg/ml)