**Case Report**

# Ligneous conjunctivitis and holoprosencephaly –a rare association

**Divya Karuppannasamy* , Vikrant Kanagaraju** , Alo Sen***

Department of Ophthalmology* and Radiology**, PSG Institute of Medical Sciences and Research, Coimbatore, India
Corresponding author: Dr.Divya Karuppannasamy

Date of submission: 10 October 2014; Date of Publication: 17 December 2014

**Abstract :**

Ligneous conjunctivitis is a rare form of bilateral, chronic, recurrent disease in which thick membranes form on the palpebral conjunctiva and other mucosal sites. Ligneous conjunctivitis has been reported to occur occasionally in association with congenital occlusive hydrocephalus. We report the association of ligneous conjunctivitis with holoprosencephaly, a rare cerebral malformation resulting from incomplete division of the embryonic forebrain which is not well known. A five month old infant with developmental delay presented to us with thickened woody membranes on the palpebral conjunctivae of both eyes. Neuroimaging studies revealed fusion of the frontal horns of both lateral ventricles, absent septum pellucidum and thin corpus callosum- suggestive of lobar holoprosencephaly. A clinical diagnosis of ligneous conjunctivitis was made and the infant was managed medically with topical heparin and fresh frozen plasma. At six months follow up there has been significant resolution of membranes and no recurrences have been noted.

**Key words :** Ligneous conjunctivitis, plasminogen, holoprosencephaly

## Introduction

Ligneous conjunctivitis is a rare form of Membranous conjunctivitis with typical woody induration of the conjunctiva. It affects mostly infants and children but the disease may manifest at any age.The disease process may also involve other mucous membranes, such as the cervix and the trachea, occasionally leading to death by tracheal obstruction.[(1)] Plasminogen (PLG) deficiency has recently been associated with ligneous conjunctivitis.[(2)]

The management of ligneous conjunctivitis is difficult and no satisfactory treatment exists till date. Surgical excision of the membranes is often followed by recurrence and treatment with heparin, fresh frozen plasma, cyclosporine and amniotic membrane transplantation have all been tried with varying degrees of success.[(3)] We reported a rare case of ligneous conjunctivitis associated with holopro-sencephaly. To the best of our knowledge no similar case has been reported in literature.

## Case report

A five month old female infant presented to our centre with developmental delay and a history of membrane formation on the palpebral conjunctiva of both upper and lower eyelids noted two months after birth. She was the only child born to second degree consanguineous parents. There was no other significant family history. The infant had already been diagnosed to have lobar holoprosencephaly by antenatal ultrasound performed on the mother at 29 weeks of gestational age and was delivered at term by lower segment caesarean section for oligoh-ydramnios.

Examination of the eyes revealed a firmly thickened, yellow, sessile, woody membrane on the upper and



www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

lower tarsal conjunctiva of both eyes.(Fig. 1) There was no involvement of the bulbar conjunctiva or cornea and posterior segment was within normal limits. Examination of other mucosal surfaces such as the gingiva, ear, throat and genital tract did not reveal any abnormality. The child did not have any other anomalies on physical examination.

Neurosonogram revealed fusion of the frontal horns of both lateral ventricles with absent septum pellucidum, while the occipital and temporal horns appeared normal.(Fig. 2)

Magnetic resonance imaging of the brain revealed fusion of frontal horns of both lateral ventricles with wide communication of the fused segment with the 3rd ventricle, absent septum pellucidum and thin corpus callosum-suggestive of lobar holopros-encephaly associated with relative hypoplasia of the white matter of bilateral cerebral hemispheres.(Fig. 3,4) The thalami, pituitary gland, cerebellum and brainstem were found to be normal.

The membranes were then removed surgically and sent for microbiological analysis and and histopathology. The patient was empirically treated with topical antibiotics and steroids. However, recurrence of the membranes was noted within two weeks.

Histopathology of the membranes revealed surface ulceration with subepithelial deposit of amorphous eosinophilic material, granulation tissue and lymphocytic infiltration. Microbiological cultures were negative.

A diagnosis of ligneous conjunctivitis was made based on the above features and the child was treated with topical heparin (5000IU/ml) and fresh frozen plasma eye drops four times a day. At 6 months follow up, there is significant resolution of the membranes and no recurrences have been noted. (Fig. 5)

**Discussion**

In this case report we have presented the association between ligneous conjunctivitis and holopros-encephaly in an infant. Because of the rarity of both conditions the association is unlikely to be coincidental.

Review of literature has revealed that ligneous conjunctivitis appears to be the ocular manifestation of a systemic disease, which might be accompanied by formation of both true and pseudomembranes on the mucosa of the mouth (ligneous gingivitis or peridontitis), the tracheobronchial tree, the kidneys, and the female genital tract (ligneous vulvovaginitis or cervicitis) as well as juvenile colloid milium in sun exposed areas.[3]Since the introduction of the term, more than 150 cases have been described in the literature.[4]However the exact prevalence is not known.

In patients with ligneous conjunctivitis, there is a major deficiency of plasmin mediated extracellular fibrinolysis that is required in the normal process of wound healing. As fibrin degradation is limited, the process halts at the stage of granulation tissue formation and subsequently forms a fibrin rich pseudomembranous tissue.[3]

Surgery without sufficient prophylactic measures (such as topical heparin) is by itself a potent trigger for recurrence of ligneous membranes, which usually reappear within a few days. Hence the number of excisions of pseudomembranes and other mechanical manipulations should be kept to a minimum, and if necessary accompanied by local treatment.

At least 16 children with ligneous conjunctivitis have been reported to coincidently suffer from congenital occlusive hydrocephalus, seven of whom had



www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

plasminogen deficiency.[3] The pathophysiologic mechanism behind the association of ligneous conjunctivitis and holoprosencephaly in our patient remains unclear. Plasminogen is converted into plasmin which regulates angiogenesis directly by degrading matrix molecules and indirectly by activating extracellular matrix metalloproteinases and angiogenic growth factors .[5] Plasminogen (PLG) thus plays an important role in intra- and extravascular fibrinolysis, wound healing, cell migration, angiogenesis, and embryogenesis.[6]

In vitro studies have revealed complex coupling between the SHH (sonic hedgehog) signaling pathway and the plasminogen/plasmin system for inducing angiogenesis.[7]

SHH gene encodes the sonic hedgehog protein, which also plays a critical role in early forebrain and CNS development.[8] Mutation of the SHH gene has been found to be the most common cause of non-syndromic holoprosencephaly, with other genes like SIX3,ZIC2 TGIF being less often implicated.[9]

Holoprosencephaly is a rare structural malformation of the developing forebrain, resulting from incomplete midline cleavage of the prosencephalon and associated with varying degrees of neurologic impairment and dysmorphism of the brain and face. Holoprosencephaly is estimated to occur in 1/10 000–20 000 live births.[10]

Deficiencies in embryonic forebrain cleavage range from the most severe or alobar forms where there is diffuse cortical non separation to the least severe or lobar form characterized by nonseparation of the basal aspect of the frontal lobes as seen in our patient.[11] Distinctive midline facial malformations like cyclopia, ocular hypotelorism, flat nasal bridge, cleft lip, cleft palate and bilateral colobomas have been reported occur in most cases of holoprosencephaly. These correlate with the degree of holoprosencephaly and have prognostic importance.[11]

A variety of teratogens such as salicylates, maternal diabetes mellitus, alcoholism, chromosome abnormalities like trisomy 13 and intrauterine infections can result in HPE.

None of the above risk factors were noted in our patient and there was no facial dysmorphism or syndromic association.

In summary, our patient had ligneous conjunctivitis associated with lobar holoprosencephaly- two rare entities in their own right. Given the role of plasminogen in embryogenesis, further studies are needed to investigate whether coupling of the SHH pathway and the plasminogen/plasmin system plays a role in neural tube development and division.

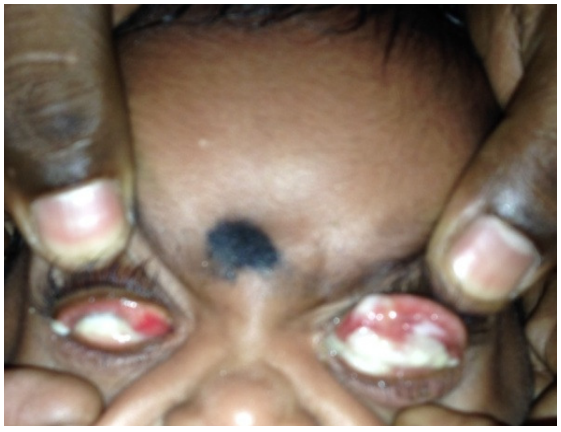

Fig 1: Clinical photograph showing thick membranes on the tarsal conjunctiva of both eyes



www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

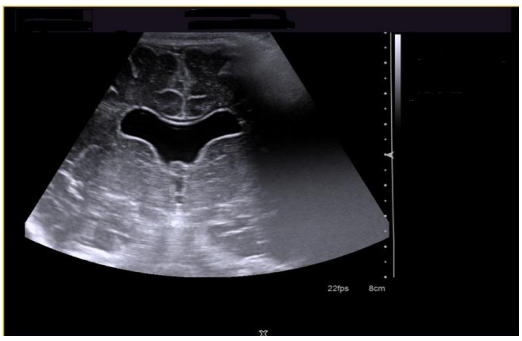

Fig 2: Neurosonogram showing fusion of frontal horns of both lateral ventricles with absent septum pellucidum.

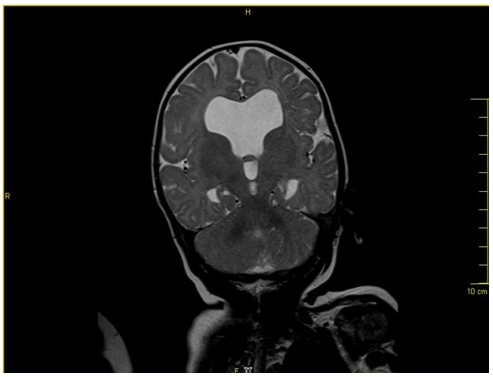

Fig 3:Coronal MR image(T2 Weighted) showing fusion of frontal horns of both lateral ventricles, wide communication of the fused segment with the 3rd ventricle and absent septum pellucidum.

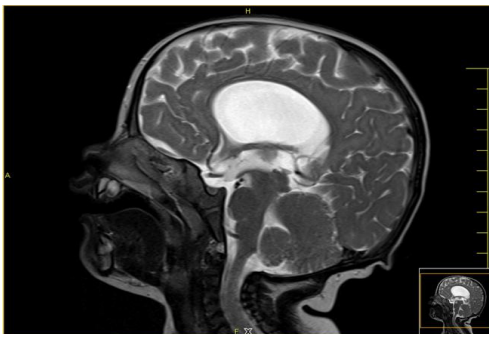

Fig 4:Sagittal MR image(T2 Weighted) showing thin corpus callosum.

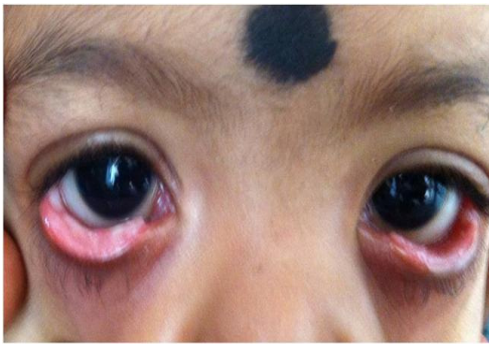

Fig 5: Follow up clinical photograph showing resolution of membranes

**References**

1. Cooper TJ, Kazdan JJ, Cutz J. Ligneous conjunctivitis with tracheal obstruction. A case report, with light and electron microscopy findings. Canad J Ophthalmol 1979;14:57–62.

2. Schuster V, Mingers AM, Seidenspinner S, Nussgens Z, Pukrop T, Kreth HW. Homozygous mutations in the plasminogen gene of two unrelated girls with ligneous conjunctivitis. Blood 1997;90:958-66.

3. Schuster V, Seregard S. Ligneous conjunctivitis. Surv Ophthalmol 2003;48:369-88.

4. Neff KD, Holland EJ, Schwartz GS. Ligneous conjunctivitis. In: Krachmer JH, editor. Cornea, 3 rd edn. New York: Elsevier Inc;2011. p. 629-34.

5. Adibhatla RM, Hatcher JF. Tissue plasminogen activator (tPA) and matrix metalloproteinases in the pathogenesis of stroke: therapeutic strategies. CNS Neurol Disord Drug Targets 2008;7:243–53.

6.Castellino FJ, Ploplis VA. Structure and function of the plasminogen/plasmin system. Thromb Haemost 2005;93: 647-54.

7. Teng H, Chopp M, Hozeska-Solgot A, Shen L, Lu M, Tang C et al. Tissue plasminogen activator and plasminogen activator inhibitor 1 contribute tosonic hedgehog-induced in vitro cerebral angiogenesis._PLoS One 2012;7(3):e33444.

8. Nagase T, Nagase M, Yoshimura K, Fujita T, Koshima I. Angiogenesis within the developing mouse neural tube is dependent on sonic hedgehog signaling: possible roles of motor neurons. Genes Cells 2005;10:595–604.

9. Savastano CP, El-Jaick KB, Costa-Lima MA, Abath CM, Bianca S, Cavalcanti DP et al. Molecular analysis of holoprosencephaly in South America. Genet Mol Biol 2014;37:250-62.

10. Dubourg C, Bendavid C, Pasquier L, Henry C, Odent S, David V. Holoprosencephaly. J Rare Dis 2007;2:8.

11. Raam MS, Solomon BD, Muenke M. Holoprosencephaly: a guide to diagnosis and clinical management. Indian Pediatr 2011;48:457-66.