A Case with Ligneous Conjunctivitis and Allergic Rhinitis

Ligneöz Konjonktivit ve Allerjik Riniti Olan Bir Olgu

Özlem ATAN ŞAHİN,[a]
Ahmet KÜÇÜKÇELEBİ,[b]
Figen GÜLEN,[c]
Sait EĞRİLMEZ,[d]
Ferda ÖZKINAY[e]

[a]Department of Pediatrics,
Acıbadem University Faculty of Medicine,
[b]Clinic of Esthetics and Plastic Surgery,
Acıbadem Maslak Hospital, İstanbul
Departments of
[c]Pediatric Allergy and Pulmonology,
[d]Ophthalmology,
[e]Division of Pediatric Genetic,
Ege University Faculty of Medicine,
İzmir

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Yazışma Adresi/*Correspondence:*
Özlem ATAN ŞAHİN
Acıbadem University Faculty of Medicine,
Department of Pediatrics, İstanbul,
TÜRKİYE/TURKEY
ozlem.naciye.sahin@acıbadem.com.tr

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ABSTRACT This is a case report of an 11- year old male patient with pseudomembraneous conjunctivitis, history of wheezing attacks, tearing, itching of both eyes and nose. His skin prick test was positive for olive pollen and cat dander. His plasminogen activity was 55%. Compound heterozygous mutations ARG216>His(R21H)+& Thr352>Ileu(T3521) were detected in the mutation analysis. The patient was diagnosed as allergic rhinitis and ligneous conjunctivitis due to plasminogen deficiency. For children with prominent conjunctivae findings in the course of allergic conjunctivitis, pseudomembraneous conjunctivitis shoul take place in the differential diagnosis.

Key Words: Ligneous conjunctivitis; pseudomembraneous conjunctivitis; plasminogen; allerjik rhinitis

ÖZET Bu olgu raporunda burun ve gözlerde kaşıntı, göz yaşarması, hışıltılı solunum atakları hikayesinin yanısıra yalancı membran oluşumu ile seyreden konjonktiviti olan onbir yaşında erkek hasta olgu sunulmaktadır. Olgunun zeytin poleni ve kedi epiteline karşı deri prik testi pozitif idi. Plasminojen aktivitesi %55 olarak saptandı. Mutasyon analizinde heterozigot ARG216>His(R21H)+ &Thr352>Ileu(T3521) mutasyonları tespit edildi. Hastada allerjik rinit ve plazminojen eksikliğine bağlı gelişmiş ligneoz konjonktivit tanısı kondu. Allerjik konjonktivit tanısı alan belirgin konjonktiva tutulumu olan olgularda, ayırıcı tanıda ligneoz konjonktivit yer almalıdır.

Anahtar Kelimeler: Ligneoz konjonktivit; psödomembranöz konjonktivit; plazminojen; allerjik rinit

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Ligneous conjunctivitis is a membraneous conjunctivitis characterized by recurrent fibrin rich pseudomembraneous lesions of woodlike consistency that develop mainly on the tarsal conjunctiva due to PLG (plasminogen) deficiency. PLG plays an important role in intravascular and extravascular fibrinolysis, wound healing, cell migration, tissue remodelling, angiogenesis and embriogenesis. PLG deficiency has been classified as (i) hypoplasminogenemia or "true" type I PLG deficiency, and (ii) dysplasminogenemia, also called type II PLG deficiency leading pseudomembrane formation on associated mucous membranes such as, respiratory tract, middle ear, eye, oral cavity, central nervous system, female genital tract and duodenum. Episodes may be triggered by trauma, surgery or by systemic events such as infections. Allergy may also be a trigger for the for-

mation of pseudomembranes in the course of the disease.

In this report an 11-year-old Turkish boy who had pseudomembraneous conjunctivitis with recurrent wheezing attacks, high IgE level and positive skin prick test for olive tree pollen and cat dander is presented. His PLG antigen level and PLG activity were low. Genomic DNA from the patient was analysed for mutations in the PLG gene and compound heterozygous mutations ARG216>His (R21H)+& Thr352>Ileu (T3521) were detected. Until now no coexistance with allergic rhinitis and ligneous conjunctivitis was reported. Patient consent form was obtained from parents of children.

CASE REPORT

An 11-year-old Turkish boy who had pseudomembraneous conjunctivitis was admitted to pediatric allergy and pulmonology clinic for nasal itching and recurrent wheezing attacks.

The patient was one of the three sons of non-consanguineous parents (Figure 1). He was born 4100 g by spontaneous vaginal delivery at 39 weeks gestation. His father was 38 and his mother was 35 years old. There was no significant medical or family history. He had recurrent wheezing episodes begining from eight months until three years old. When he was 5 years old he had conjunctivitis with prominent tarsal conjunctivae involvement, sneezing, tearing in both eyes and nasal discharge. His symptoms were all year round but tend to be severe in spring time. Edema of the eyelids with pseudomembranes of wood like consistency was mainly observed when he was 8 years old (Figure 1). He was evaluated for conjunctivitis in the ophthalmolgy clinic and was diagnosed as pseudomembraneus conjunctivitis. He was referred to pediatric allergy and pulmonology department for chronic tearing from both eyes and wheezing episodes. His height was 146 cm (50-75 p), weight 33 kg (25-50p), respiratory rate: 18/min, he had anterior servical microlymphadenopathy, bilateral conjunctivitis with palpebral pseudomembranes. Chest sounds were normal. He had pectus excavatum. Cardiac sounds were normal. His pulse was 92/ min and blood pressure, 100/60 mmHg. No organo megaly was identified. Neurological examination was normal. Chest X-ray and echocardiography were normal. Cranial magnetic resonance imaging (MRI) was normal excluding intracranial manifestations of the disease such as occlusive hydrocephalus. At first evaluation his inhalent specific IgE was ++. Skin prick testing was performed at Ege University Pediatric Allergy and Pulmonology Department. Alyostal ST-IR (Stallergenes S.A. France) was used for skin prick testing. Antihistamine drugs were stopped ten days before skin prick testing. After cleaning forearm with 70% alcohol, allergens were applied by Stallerpoint needles with one drop standard dose. Test result was evaluated after 20 minute reaction time. For negative control 0.9% NaCl was used, for positive control histamine hydrochloride was used. Enduration diameter larger than >3mm was designated as a positive test result. Enduration diameter smaller than 3 mm was

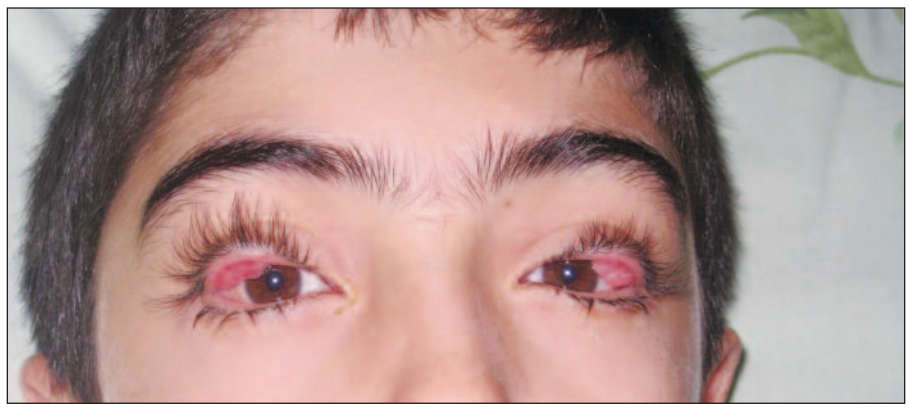

FIGURE 1: Pseudomembranes on tarsal conjunctivae.

designated as a negative test result. Allergens used in skin prick test was as follows; dander *Felix domesticus, Oleaceae, Aspergillus mix (Aspergillus fumigatus, A. nidulans, A. niger), Cladosporum (Cladosporium cladosporioides, C. herbarum), Penicillium Mix (Penicillum digitatum, P. expansum, P. notatum), Alternaria alternata, Rhizopus nigricans, Mucor racemosus, D. pteronyssinus, D. pharinae, Acarus siro, Glyciphagus domesticus, Lepidoglyphus destructor, Tyrophagus putrescentiae, Paspalum notatum, Hordeum vulgare, Agrostis vulgaris, Cynodon dactylon, Weed Mixture, Zea mays, Festuca eliator, poa pratensis, Avena sativa, Secale cereale, Lolium perenne, Anthoxantum odoratum, Phleum pratense, Triticum vulgare, Holcus lanatus, Taraxatum vulgare, Chenopodium album, Artemisia vulgaris, Urtica doica, Chrysanthemum leucanthemum, Plantago, Ambrosia elaitor, Salsola cali, Rumex acetosa, Parietaria officinalis, Rough pigweed, Golden rod, Almus glutinosa, fraxinus excelsior, Fagus sylvatica, Betula alba, Castenea vulgaris, Juniperus asheesi, Cup, Ulmus campestris.* Skin prick test result was positive for olive pollen 6 mm (2+) and cat dander 8 mm (3+). He had a cat dander contact and there have always been olive trees around. Respiratory function tests were normal as his FVC: 91%, FEV: 104%, MEF 25-75: 133%. Bronchial provacation test with metacholine revealed a fall in FEV1 from 90% to 70% at 0.031 mg/ml concentration.

The child was suffering from conjunctivitis of both eyes. He had pseudomembranes in tarsal conjunctiva and tearing on both eyes. The remaining ocular examination was normal. Laboratory tests revealed that the PLG functional activity was 55%. So we decided to perform the mutation analysis for the patient. He was compound heterozygote for the mutations ARG216> His(R216H) + & Thr352> Ileu (T3521). He did not have any respiratory system findings other than wheezing and nasal itching episodes. Cranial MRI was normal excluding hydrocephalus as the central nervous system manifestation of the disease. Leucotrien receptor antagonists (LTRA) was the first choice controlling medication. After LTRA, attacks were under control. A year later he was succesfully treated with topical plasminogen and amniotic membrane transplantation in the ophthalmology department. Authors of this study obeys the ethical principles of Declaration of Helsinki.

DISCUSSION

Inherited homozygous or compound-heterozygous hypoplasminogenemia is a very rare disorder with an incidence estimated at below 1: 1000 000.[1] Ligneous conjunctivitis is one of the cardinal manifestations of hypoplasminogenemia. Periodontal tissue, the upper and lower respiratory tract, middle ear, kidneys, central nervous system and female genitalia may be involved in the patients with hypoplasminogenemia. Congenital heterozygous hypoplasminogenemia is a rare event first described in 1982 in a patient with thromboembolic disease. The disease was first reported by Biusson and the term 'conjunctivitis lignosa'or '' ligneous conjunctivitis'' was first used by Borel in 1933.[2,3] Most cases are sporadic although an autosomal recessive inheritance pattern has been described. First, Mingers et al. showed that the disease was inherited by type I plasminogen deficiency in 1994 and showed that it is strongly associated with homozygous or compound heterozygous type-1 plasminogen deficiency.[4] The gene has been mapped to chromosome 6q26- q27. It spans about 52.5 kilobases (kb) of DNA and consists of 19 exons and 18 introns. The PLG cDNA of 2.7 kb encodes a protein consisting of 791 amino acid residues.[5] In report of Tefs et al. in 2006 reviewing the molecular and clinical spectrum of 50 patients, the most common genetic alteration was K19E mutation in 34% of the patients, plasminogen plays an important role in extravascular and intravascular fibrinolysis.[6,7] Plasminogen is synthesized primarily in the liver; it converted into a potent proteolytic enzyme, plasmin, through either plasma or tissue activators, and breaks down the fibrin cloth to its soluble degradation products. Conjunctiva is an extrahepatic site for plasminogen synthesis. Histological findings of the disease are amorphous subepithelial deposits of eosinophilic material consisting predominantly of fibrin. Plasminogen activators released by tissues convert plasminogen in to

plasmin and fibrin deposits of all body fluids are eliminated by fibrinolytic system. Plasminogen (plg) deficiency has been classified as (i) hypoplasminogenemia, and (ii) dysplasminogenemia. Dysplasminogenemia does not have any specific clinical manifestation while severe hypoplasminogenemia is associated with defective fibrin clearence during wound formation. Pulmonary involvement in the course of the disease may be fatal.

Respiratory tract involvement with pseudomembranes is a common manifestation of the disease. Further manifestations including upper and lower respiratory tract are nasopharynx , middle ear, gingiva, larynx, trachea, vagina and cervix.[8] The fibrin deposits impair the tracheobronchial tree ciliary system and this predisposes the patient to significant infections in the sinuses, middle ear and tracheobronchial tree.[9] In a report of Tefs et al., %30 percent of 50 patients with LG had respiratory tract involvement.[6] Plasminogen has been found as an important regulator in the pathogenesis of murine model of asthma. Plasminogen plays an important role in cell migration and is also implicated in tissue remodelling. Swaisgood et al. reported that plasminogen plays an important role in asthmatic response.[10]

It has been established that PAI- 14G allele may be a genetic risk factor for childhood asthma in Turkish children in 2001 report of Bora and Ercal. In this study part of the patients had family history of atopy and part did not.[11] In another study the plg- knockout (plg - / -) mice were independently generated by two research groups.[12,13] The clinical manifestations of these animals were indistinguishable from ligneous conjunctivitis in humans with severe hypoplasminogenemia. Thirty nine percent of them developed pulmonary lesions, 23% tracheal thrombi and 8% laryngeal thrombosis as respiratory tract involvement. Our case did not develop any respiratory findings other than nasal itching and wheezing episodes. As conclusion a allergic rhinitis and asthma should be kept in mind in children with ligneous conjunctivitis with respiratory system findings. Variations in the gene encoding plasminogen may be associated with allergy succeptibility in children with plasminogen deficiency which has to be studied further.

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