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Case Report

Laryngo-onycho-cutaneous (LOC) syndrome; Long Term Outcomes of Two Patients with laryngeal Involvement

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ABSTRACT

Abstract: Laryngo onycho cutaneous (LOC) is a very rare autosomal syndrome with the majority of patients from Punjab. Although LOC syndrome is now a subtype of Junctional Epidermolysis Bullosa(JEB-LOC), JEB-LOC has a distinct clinico-pathologic appearance and molecular fingerprint. The intricacies of the JEB-LOC subtype are discussed in this article with regard to disease presentation, pathogenesis, management, and prognosis. Methods:Two female siblings were diagnosed to have LOC syndrome. Within months of birth, patients developed an overgrowth of abnormal granulation tissue. Patients were followed till the age of 24. The most severely affected case was diagnosed as a tuberculosis' patient , and treated with 9 month course of anti-Tb medication. However, the other case received Isonizide as prophylactic for three months. Results: In our case, multiple strategies had been applied (Bronchoscopy, KTP laser, Kitomycin, Montgomery sling) and using anti-tuberculosis medications for both sisters showed obvious prolonged survival compared to other similar cases that have been reported to die in earlier age. Conclusion: Whether anti-tuberculosis medication has an influence of the survival rate to LOC syndrome as granulations disease or not, further study and recommendations needs to be done.

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INTRODUCTION

LOC syndrome has been recently represented as a subtype of junctional epidermolysis bullosa (JEB) with autosomal recessive genetic aberration. LOC syndrome presents with distinguished skin and mucous membranes excessive granulation tissue formation that may lead to delayed wound healing, laryngeal airway obstruction and visual impairment which will result in blindness. So far, most cases are confined to Punjabi ancestry and are shown to result from a founder mutation within the LAMA3 gene, especially involving a unique nucleotide insertion mutation in DNA39, that is restricted to the LAMA3A (designated DNA one of LAMA3A) [1].

LOC syndrome results from disturbed laminin synthesis in skin and mucosal basement membrane. The responsible mutation antecedentlyknownin agene on chromosome18 that encodes laminin alpha 3a[2]. The multisystem disorder is characterized by formation of excessive granulation tissuewithin thecorium and submucosa at sites of continual trauma or pressure, like the skin of elbows, knees and digits, and also themucosal membranes tissues of the vocal cords and conjunctiva[3].

The syndrome is confined to Punjabi Muslim population in West Pakistan wherever high degree of consanguinity is practiced. The first to report such disease was Shabbir in 1986, in 22 patients' cases, all of whom suffered from considerably similar clinical presentation that had not been described before and consequently named Shabbir's Disease[3].

Such patients suffer common clinical presentation. The earliest symptom is husky cry immediately after birth;despite those neonates physically have no abnormalities. Owing to defective laminin and repeated trauma, granulation tissue develops within the mucosal membranes including the larynx and nail beds. Conjunctival lesions and chronic skin ulcers start appearing in early childhood. Though original Shabbir description of LOC syndrome did not entail ocular involvement[3], ocular granulation tissue like a very aggressive pterygium has been reported altogether later patients described[4-6] and was a prominent feature within the patients studied. Additionally, there's failure of enamel formation[4-6] and marked dental malformations3. The short life expectancy of LOC syndrome sufferers that they don't live on the far side childhood, the foremost common reason for premature death being acute or chronic respiratory obstruction accompanied withsecondary pneumonia[4-6]. However, patients who manage to survive the early childhood period typically survive to adulthood, as observed by A.D. Irvine and C.S. Munro, and symptoms of huskiness and ulceration slowly subside[3]. A permanent tracheostomy typically becomes essential to ensure patent respiratory airways caused by after accumulation of granulation tissue within the larynx. Additionally, granulation tissue mayspread to the epiglottis, trachea[5] and even the main bronchi[6]. What is more, most of the older patients studied are blind owing to corneal pterygium formation.

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Death will result via fatal respiratory obstruction and pneumonia[7]. Different surgical interventions are accustomed to relieve obstruction like tracheotomy, gastrostomy, suprapubic catheterization are all performed throughout the first decade of life to halt the ensuing laryngeal, gastrointestinal, and urethral strictures, respectively[7].

Antibiotics, corticosteroids, dapsone, and anti-tuberculosis medicines have marginal long-term advantages in this patients' population. Encouraging results were achieved, however, with vascular laser intervention for laryngeal involvement in non-Punjabi patient with LOC within the face of respiratory obstruction. What's distinctive concerning management of LOC is that the severe eye involvement; thalidomide has been trialed to reduce granulation tissue. Also amniotic membrane transplantation has been accustomed reduce ocular scarring[7].

Over the last 4 decades Saudi Arabian economy showed continuous growth, this attracted immigrants from different neighboring countries. I am describing 2 patientswith LOC syndrome who presented in Saudi Arabia in my institute with laryngeal involvement and their outcomes

Case Reports

Case 1

A threemonths old Muslimgirl,from Punjab region, presented to the department of ENT at King Abdulaziz university hospital the parent main complaining was the her weak cry.She was born in 1989 of first degree relative parents. Examination of the upper airway revealed a laryngeal mass, thickening of the vocal cord and laryngeal wall with some sort if laryngeal web. Surgical excision of the mass was performed followed by histopathological examination that revealed underlying pathology was granulation tissue of unknown etiology. The main reason for coming back to the clinic was the thickening of both hand and feet nail bed, with bleeding of a small collection of granulation tissue.At the age of 7 months, she presented to the ophthalmologist with granulation tissue formation in the lateral fornix of the left eye and bilateral corneal ulceration. The disease progressed over 9 years, the eyes and larynx were infiltrated by granulation tissue and caused obstructions that necessitate tracheostomies and multiple OR admissions to release the adhesions and conjunctival reconstruction by amniotic membrane graft.

In addition, she had a yellowish discoloration of her teeth due to absence of an enamel coating. At the age of 10 years old she was diagnosed to have LOC syndrome. At thattime, she received prophylactic anti TB medication (INH) for 3 months, because her sister was diagnosed to have Tuberculosis. She was followed up until the age of 23 years old, and after that she went back to her country. She is now 26 years old and completing her education.

Case 2:

A Punjabi Muslim girl, was born in 1988 of healthy Muslim parents were first cousins presented at birth with weak cry and stridor due to 80% vocal cord paralysis .At two months of age she suffered from recurrent fungal nail infections and dystrophies, and it became worse as she was getting old. Some of the nails were absent with replacement of granulation tissue and some had blackish discoloration with spontaneous bleeding. In the ensuing months, she developed overgrowth of granulation tissue in both eyes (lateral fornices), with recurrent OR admission to release adhesions.

The disease progressed (recurrent laryngeal webs, severe subglottic stenosis, and recurrent vocal cords masses) and later a tracheostomy was necessary due to increasing respiratory distress. Multiple procedures and techniques were done in order to remove the infiltrated granulation tissue to keep the airway patent.

At the age of 11 years old, diagnosed as LOC syndrome patient. She also had relevant history of pulmonary tuberculosis and received 9 months course of anti- tuberculous therapy (INH, Rifampcin, Klacid and Pyrazanmide). Also her mother and sister started INH prophylaxis. She is now 27 years old and completing her education.

Discussion:

The present patients' cases clearly demonstrate that airway is severely affected in patients suffering with LOC syndrome. The illness is characterized by production of vascular granulation tissue, which ends up in destructing specific epithelium like the conjunctiva, corneal epithelium, skin ulceration, nail abnormalities and respiratory mucosa[6,8]. They're vulnerable to pneumonia. These locations of tissue erosions of the laminin a3A are almost like the clinical manifestations of JEB-LOC[9].

The responsible mutation was found to be homozygosity mutation in laminin a3 gene (LAMA3). A basal keratinocytes within the skin and alternative stratified epithelia secrets a basement membrane laminin[2]. The basal keratinocytes secrete the abbreviated a3 chain thatends up in disturbance in extracellular matrix homeostasis[10]. This abnormality permits a site for erosion on the membrane membranes, as well as nail bed, and all over to the larynx[3].

Although patients with LOC syndrome aren't responding to chemotherapeutics, treatment with corticosteroids, Antibiotics, anti-tuberculosis medications and dapsone has shown a marginal long term advantage[7].

Several Surgical interventions are used throughout the patient childhood amount like tracheostomy, gastrostomy, and supra-pubic catheterization so as to arrest the ensuing laryngeal, gastrointestinal, and urethral strictures. However, using laryngeal vascular laser approach in LOC syndrome with respiratory obstruction has promising result[7].

In fact, patients with LOC syndrome have a high death rate throughout childhood. The leadingreasons behind death are pneumonia and fatal respiratory obstruction. Except for people who survived, several patients had remission within the second decade[7].

In our case, multiple approacheshad been applied (bronchoscopy, KTP laser, kitomycin, montgomery sling) and using anti-tuberculous medications for bothsisters showed obvious prolonged survival compared to alternative similar cases that are reported to die in earlier age.

It's been proved that tuberculosis has a human genetic susceptibility[3]. It was found to be an evidence of genetic influence at the level of the innateimmune response[2,6,8,10]. Agenome-wide association scansfound an association in the gene-poor region onchromosome 18q11.2[3,6].

According to the recent researches ,the predisposing gene of tuberculosis is 18q11.2; we observed that LOC syndrome and

tuberculosis shared the same gene. So, there is maybe a positive correlation between using anti-tuberculous medication and improving the state of LOC syndrome survival rate.

Conclusion

In conclusion, whether anti-tuberculous medication has an influence on the survival rate to LOC syndrome as granulations disease or not, further studies and recommendations needs to be done.

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