

A Study of Awareness and Knowledge about Epidermodysplasia Verruciformis-A Genetic Disorder



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Abstract: Tree man syndrome is a rare inherited skin disorder, including persistent infection caused by human papillomavirus, as a result of which a defect in cell-mediated immunity takes place. This infection results in the growth of scaly macules and papules, mostly on the feet and hands. It is a lifelong disorder that can be treated in surgical and non-surgical ways. A questionnaire or awareness-based study was conducted among the population of Karachi, Pakistan (both medical and non-medical). It was attended by 506 individuals. To raise the consciousness of this illness. The questions evaluated their knowledge of tree man illness, the possible consequences of the condition and the latest therapies. More than 80% of people were totally unaware of tree man disorder. Only 10% of people were aware or just heard about this disease. The awareness of Tree man syndrome was very low among the people. Steps should be taken to increase awareness about this rare but life-threatening disease.

Key Words: Tree Man Syndrome, Lewandowsky-Lutz, Awareness

Introduction

Tree man syndrome is also named Epidermodysplasia Verruciformis or Lewandowsky-Lutz. This syndrome was first recognized as an epidermal nevus by Lewandowsky and Lutz in 1922. [Schgal, VN, Luthra A, Bajaj P. (2002)] It is an autosomal recessive inborn hereditary illness of human derma associated with a high risk of squamous cell carcinomas. This is named as tree man disorder by reason of sufferer having this illness suffer from a body covered with warts like lesions that resembles a tree. The sufferer shows

immunodeficiency and susceptibility to infections caused by the human papillomavirus. [Orth, G. (1986), Lutzner, MA. (1978)] More than a hundred diverseness of human papillomaviruses are discovered, which shows asymptomatic activities in healthy individuals. These viruses can cause skin or mucous membrane growth (warts) and can cause various forms of carcinomas. [Androphy, EJ, Dvoretzky, I, Lowy, DR. (1985)]



Figure 1: A patient suffering from Epidermodysplasia verruciformis. (Hague, J.E., & Crosby, E.L. (1948))

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Epidermodysplasia Verruciformis (EV) is an inborn illness as well as a huge rate of familial incidence that is characterized by a lifelong generalized explosion of skin lesions that imitate flat warts; a malignant transformation for some of the lesions is seen in around 25% of EV cases, typically on sun-exposed areas. [Hague, J.E., & Crosby, E.L. (1948)] The wart-like lesions are contagious, and intranuclear papillomavirus particles are often seen in benign lesions but are no longer seen in carcinomas. In the

pathogenesis of EV, inborn, immunological, and extrinsic features all play a part. However, the virus's function, particularly in the malignant transformation, is unknown. For a long time, it was assumed that all human lesions because of papillomavirus were caused by the same strain. The presence of two distinct forms of human papillomavirus (HPV) with no, if any, DNA sequence homology and no antigenic cross-reaction was, however, discovered. [Lutzner, MA. (1978)]



Figure 2: Bark like growth on hands of a patient suffering from tree man syndrome. [Harris, J.J. (1966)]

Background

Epidermodysplasia is a condition that affects the skin. The first case of Epidermodysplasia verruciformis (EV) was identified in 1922. Warty papules, plaques, or scaly maculae appear before infancy and gradually spread across the body. Lesions on the dorsum of the hands and wrists are common, but they can also affect the scalp, expression, shoulders, and arms. The Koebner syndrome can be present in lesions that mimic verruca plana. Both of the genders are affected together; congenital parents and mental obstruction are common, and family members are usually affected. Hyperkeratosis as well as basket-weave design, hypertrophy of the stratum granulosum, vacuolation of both the granular and prickle cell covers, pyenosis, and acanthosis are all histological characteristics of EV. Basal cell carcinoma, squamous cell carcinoma, and intermediate stages of malignant degeneration are examples of malignant degeneration (Pagetoid, basosquamous, Borst-Jadassohn). 2 Because of its resemblance to generalized verruca plana, there is debate over whether EV should be classified as a separate disease. [Hague, J.E., & Crosby, E.L. (1948)] Lutz, the coauthor of the initial study on EV, looked at two sisters who had been diagnosed with the disease.

Lutz inoculated minced lesions through abrasions on the patient's (and his personal) antecubital fossa after observing fresh lesions occurring in locations of cutaneous damage in the younger sister. The patient developed disease-like lesions, but his inoculation site only developed a short-lived lesion. Rather than EV, he settled that the two daughters had generalized warts. [Harris, J.J. (1966)]

Heredity

EV may occur infrequently or as an inherited condition. The findings of multiple retrospective experiments back up this genetic trend. About 25 percent to 50 percent of recorded EV cases in the immune-competent population have been autosomal recessive. [Sun, XK, Chen, JF. & Xu, AE. (2005)] In a study of 147 EV case files, 10% resulted in people who had consanguineous parents. [Zavattaro, E, Azzimonti, B, Mondini, M. et al. (2008)] This observation was supported by a 2002 study by Sehgal and colleagues, who found 30% in the occurrence of EV in relations to EV patients. An X-linked pattern of inheritance was discovered in a case series concerning a single, large family, and additional large relatives had

multiple cases of EV, both of which resulted in female relations. [[Genetics](#)].

According to the literature, EV has no geographical or gender predisposition. EV, geography, and gender have a connection, despite the fact that our study example is too limited to represent the whole population. Four of our seven cases were from Turkey's eastern Anatolia area, and four of the seven were male. [[Lazarczyk, M. Pons, C. Mendoza, J.A. Cassonnet, P. Jacob, Y. & Favre, M. \(2008\)](#)].

Physiology

The skin response of EV to human papillomaviruses is irregular (HPVs). Skinny macules and papules appear as a result of uncontrolled HPV infections, mainly on the hands and feet. The lesions can remain the same for many years or change shape and color. [[Ramoz, N. Rueda, J.A. Bouadjar, B. Montoya, L.S. Orth, G. & Favre M. \(2002\)](#)] With the discovery of alterations in the EVER 1 and EVER 2 genetic factor, the pathophysiology of Epidermodysplasia Verruciformis has been attributed to a lack of cell-mediated immunity. Their gene products are endoplasmic reticulum-localized integral membrane proteins. Though the role of the EVER 1 and EVER 2 genetic factor in Epidermodysplasia Verruciformis pathogenesis is unknown, one theory is that they are add in the regulation of HPV infection within keratinocytes or in the immune answer to the infection. Intracellular zinc homeostasis, which is planned by a complex of EVER proteins and active zinc proteins, might be involved in EV-HPV expression inhibition. Though 25% of estimated patients with Epidermodysplasia Verruciformis do not have EVER 1 or EVER 2 mutations, and the inherited deficiency in these patients has yet to be identified. 22 Patients with Epidermodysplasia Verruciformis who have changes in other genes have been identified in sporadic studies. Two siblings with an Epidermodysplasia Verruciformis phenotype and disrupted T-cell receptor (TCR) signalling are homozygous for an alteration that produced a stay codon in the homolog gene family member H (RHOH) gene in 2012. [[De Jong, S.J. et al., \(2018a\)](#)] A 19 years old woman with an autosomal receding MST 1 (or STK 4, serine/threonine kinase 4) deficiencyf8b who had Epidermodysplasia Verruciformis with a global immune deficiency, as well as susceptibility to other bacterial and viral infections, was also defined. MST1 deficiency causes naive T-cell lymphopenia and

compromised mature T lymphocyte egress from the thymus to subordinate lymphoid organs, as well as a reduced chemotactic reaction to multiple Chemokines, with the CCR7 ligands CCL19 and CCL21. [[De Jong, S.J., et al., \(2018b\)](#)] Finally, three siblings without EVER1/EVER2 mutations and atypical Epidermodysplasia Verruciformis were shown to have a homozygous joining defect in the genetic factor encoding LCK (lymphocyte-specific kinase), resulting in the removal of 3 exons of this gene. [[Przybyrszewska, J., A. Zlotogorski, & Y. Ramot, \(2017\)](#)] T-cell abnormalities and Epidermodysplasia Verruciformis phenotype, with skin diseases, were found in these three siblings. These findings suggest that Epidermodysplasia Verruciformis can be caused by a variety of genetic defects and that the genetic factor that causes T-cell effects play a permissive role in causing the Epidermodysplasia Verruciformis-associated HPV to cause skin lesions. The bulk of Epidermodysplasia Verruciformis cases are associated with immunosuppression, like HIV deficiency, organ transplantation, or idiopathic lymphopenia, according to research. [[Cougoul, P. et al., \(2015\)](#)] The condition of EVER 1 or EVER 2 has not been assessed in cases of achieved Epidermodysplasia Verruciformis, like HIV infection or organ transplantation. It's unclear if these patients had previously undetected defects, epigenetic modifications, or seam alternatives of EVER 1 or EVER 2, but it's apparent that global immune suppression causes the phenotype to form in these situations. Zavattaro et al. described an unusual situation of Epidermodysplasia Verruciformis in which the patient had clinical aspects of the disease but did not have the EVER1 or EVER2 mutation. 27 At the time of diagnosis, this patient was elderly and had not premalignant or malignant lesions on inspection. [[Gül, Ü., et al., \(2007\)](#)] Faulty Fas protein activity (CD95, apoptosis receptor) was discovered alongside perforin genetic variants, implying that the two factors together caused enhanced susceptibility to HPV infection due to faulty viral clearance. Furthermore, a deep CD8+ T-cell lymphocytopenia was discovered, a discovery previously reported by Azzimonti et al. in a patient with epidermodysplasia verruciformis but no EVER1 or EVER2 changes. The Papovaviridae family includes the papillomavirus genus. [[Myers, D.J. & Fillman, E.P. \(2019\)](#)].

Causes

More than fifteen diverse types of human papilloma

viruses can cause tree man syndrome. Along which HPV5 and HPV8 are the most common and are detected in 80% of cases of epidermodysplasia verruciformis. [Kim, C. et al., (2016)]

EVER1 or TMC6 and EVER2 or TMC8 are two adjacent genes found on chromosomes. They involved in the sharing of zinc in the cell nuclei and viral replication. Mutation in these genes causes tree man syndrome, as a result of which human papillomaviruses shows symptoms in the sufferer. [De Jong, S.J., et al., (2018b), Kim, C., et al., (2016)]

Sign and Symptoms

Clinical diagnostic features are eternal or long-lasting includes hypopigmented or hyperpigmented flat warts like papules, plaques which can be irregular or reddish-brown in colour, seborrheic keratosis similarly lesions, pityriasis Versicolor such as macules on the trunk, face, ears, hands and feet, usually on the areas which are highly exposed to the sun. [Przybyszewska, J., A. Zlotogorski, & Y. Ramot, (2017), de Oliveira, W.R., et al., (2015)]

The kind term of EV causes only thin, wart-like lesions to appear all over the system, while the malignant form causes polymorphic skin lesions and the growth of numerous cutaneous tumors [de Oliveira, W.R. et al., (2015)].

In patients with compromised cell-mediated immunity, an EV-like syndrome has recently been identified, and the word "acquired EV" has been coined. Immunocompromised patients with human immunodeficiency virus organ transplantation, lepromatous leprosy, Hodgkin's illness, universal lupus erythematosus, mutual variable immunodeficiency warts, immunodeficiency, lymphedema, anogenital dysplasia syndrome (WILD syndrome), immunoglobulin M deficiency, adult T-cell leukaemia, and graft-versus-host disease have all.

Diagnosis

It may be difficult to make a diagnosis with an inherited or rare disorder. For making a decision, healthcare workers look at a person's medical past, symbols, face to face papers, and laboratory test results—the following resources including guidance on this condition's diagnosis and testing. Skin biopsy is done that shows hyperkeratosis or hypergranulosis of the enlarged epidermis, the presence of human papillomavirus is also the diagnostic feature of epidermodysplasia verruciformis.

Treatment & Management

Epidermodysplasia verruciformis is incurable however symptomatic treatment can be done. Surgical excision of abnormal lesions is the temporary treatment of choice, though the lesions may never come back or may take long time to return. [Sun, X.K. Chen, J.F. & Xu, A.E. (2005)] whereas, the other treatment modalities include photodynamic therapy, systemic retinoid, cryotherapy, 5-fluorouracil interferon-alpha, topical imiquimod and 5-aminolevulinic acid. Preventive measures includes avoidance of sun exposure and photoprotection. [Zavattaro, E. Azzimonti, B. Mondini, M. et al. (2008), Genetics]

Method

A questionnaire or survey-based study was conducted among the population of Karachi, Pakistan. In order to increase the awareness about tree man disorder including the potential complications of the disease and the treatments available currently. The questions tested the awareness of epidermodysplasia verruciformis was circulated among the population of 506 people belongs to both medical and non-medical field. In order to analyze the data descriptive statistics was applied on the data by using SPSS 20.

Results

Table 1 summarizes the awareness and knowledge about tree man disorder among the population of Karachi, Pakistan. About 506 people participated in this, out which 114(22.5%) people was aware, and 392(77.5%) respondents were unaware of this disease. 67 (13.2%) respondents knew the scientific name of this whereas, 439(86.8%) had no idea. Furthermore, 96(19%) participants knew that this infection outcomes in the growth of scaly macules and papules, mostly on the feet and hands, and 410(81%) were unaware of it. 77(15.2%) respondents knew its sign symptoms such as hyper and hypopigmentation, pityriasis and flat warts like papules. Whereas 429(84.5%) were unaware of it. 107(21.1%) knew that why it is named as tree man disorder while 399(78.9%) were not. 68(13.4%) respondents had knowledge about the cause of tree man disorder, and 438(86.6%) had no knowledge. 82(16.2%) participants knew that it is a lifelong disorder and can be treated in a surgical and non-surgical way, and 424(83.85%) had no knowledge about it. Only 61(12.1%) had seen this disease in their life on the

internet or somewhere whereas, 445(87.9%) participants had never seen this disease in their life. Furthermore, 99(19.6%) had heard the name of tree

man syndrome in their life, while 407(80.4%) respondents had never heard the name of this disease in their life.

Table 1.

KMO and Bartlett's Test		
Kaiser-Meyer-Olkin Measure of Sampling Adequacy.		.789
Bartlett's Test of Sphericity	Approx. Chi-Square	229.497
	df	45
	Sig.	.000
Reliability Statistics		
Cronbach's Alpha	N of Items	
0.862		10

The Kaiser-Meyer-Olkin Measure of Sampling Adequacy is a measure that indicates a significant 0.789 values for KMO, which suggests that the data of

the questionnaire is adequate. Furthermore, the reliability of data is calculated in Cronbach's alpha which values 0.862, suggesting that data is reliable.

Table 2.

S. No	Variable	Yes	No	p-value
1.	Do you know about tree man disorder?	144 22.5%	392 77.5	0.000
2.	Do you know the scientific name of tree man disorder (Epidermodysplasia Verruciformis)?	67 13.2%	439 86.8%	0.000
3.	Do you know that it is a rare Skin cancer and genetic disorder?	114 22.5%	392 77.5%	0.000
4.	Do you know that this infection results in the growth of scaly macules and papules, mostly on the feet and hands?	96 19%	410 81%	0.000
5.	Do you know its sign and symptoms are hyper and hypopigmentation, pityriasis and flat warts like papules?	77 15.2%	429 84.5%	0.000
6.	Do you know that this is named As tree man disorder by reason of sufferer having this illness suffer from a body covered with warts like lesions that resemble tree?	107 21.1%	399 78.9%	0.000
7.	Do you know that it is caused by human papilloma virus?	68 13.4%	438 86.6%	0.000
8.	Do you know that It is a lifelong disorder that can be treated in the surgical and non-surgical way?	82 16.2%	424 83.85	0.000
9.	Have you ever seen this disease in your life?	61 12.1	445 87.9	0.000
10.	Have you ever listen the name of this disease in you life?	99 19.6%	407 80.4%	0.000

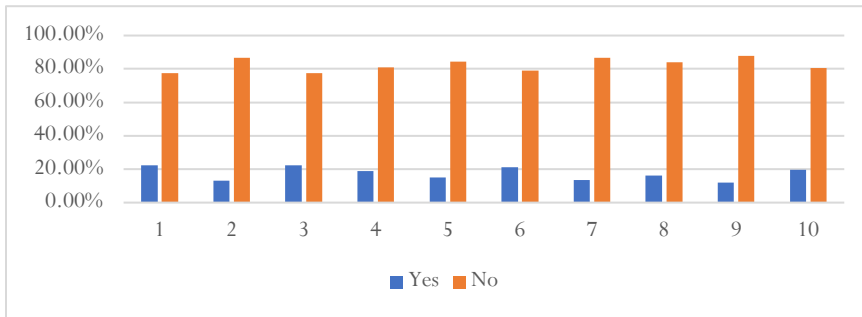


Figure 3:

Conclusion

The awareness of Tree man syndrome was very low among the huge population who belongs to both medical and non-medical field. Significant Steps should be taken to increase awareness about this rare and life-threatening syndrome. The awareness regarding its symptoms, epidemiology, causes,

prevention, as well as about the various treatment options available for tree man syndrome. The awareness among the medical staff should be increased regarding tree man syndrome by conducting health education programs or awareness-based seminars among the population regarding this genetic disorder in order to increase the knowledge or prevention among the individuals.

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