A survey study with assessment of esophageal screening and genetic counseling in patients with Howel-Evans syndrome

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Abstract

Background: It is important to better understand the role that environmental risk factors play on the development of esophageal cancer in Howel-Evans families. Additionally, there is little published about appropriate esophageal cancer screening practices in families genetically confirmed to have this condition.

Methods: Surveys were distributed to 47 addresses of an American family with Howel-Evans syndrome, of which 29 responded and met inclusion criteria. Data was collected about demographics, environmental risk factors, and medical history of participants.

Results: We report characteristics of family members with tylosis, rates of esophageal cancer, rates of genetic counseling, and levels of environmental risk factors. Of the survey respondents, 43% reported features of tylosis, 71.4% were male and 28.6% were female and 28.6% reported leukoplakia. Only 21.4% of tylotic family members smoked, 65% drank alcohol and 28.6% drank well water. More than half (57.1%) of the tylotic individuals had never had an esophagogastroduodenoscopy and no one had been diagnosed with esophageal carcinoma. Only 3.4% of respondents had ever received genetic testing for Howel-Evans syndrome, despite genetic confirmation of their relatives.

Conclusion: We encourage dermatologists to discuss smoking-cessation, genetic counseling, and early EGD with affected families.

Keywords: Howel-Evans syndrome, tylosis with esophageal cancer, palmoplantar keratoderma, esophageal cancer, leukoplakia

Introduction

Howel-Evans syndrome is a rare, unique disease, with most of the available published data based on a few affected families, one genetically confirmed from England, one from Germany, and the other from the United States. This syndrome is caused by a mutation in the *RHBDF2* gene, clinically presenting with focal palmoplantar keratoderma (PPK) over areas of pressure and friction, oral leukoplakia, and an increased risk of developing esophageal cancer. Recent literature has questioned how environmental factors impact genetically predisposed patients in subsequently developing cancer.

Howel-Evans syndrome, or tylosis with esophageal cancer, is an autosomal dominant keratoderma originally described in 1958 by Howel-Evans in Liverpool, England [1]. This original report found that 95% of those affected with tylosis would subsequently develop esophageal cancer by age 65 [1, 2]. Additionally, there is often an associated oral mucosal leukoplakia.

Thirty-five years later, Marger and Marger documented the first American family with this syndrome, including 24 individuals over five generations [3] that was subsequently expanded to include 125 individuals spanning 7 generations [4].

Esophageal cancer in this American family was reported at a lower incidence and with a later age of onset than other affected families. Among those that were affected with cancer, there was a high prevalence of tobacco use [4].

Case Synopsis

Methods

An offspring of this same, previously published American family with Howel-Evans syndrome is a patient in our dermatology clinic and helped us design a survey study approved by the University of Louisville Institutional Review Board. He had genetic testing confirming his diagnosis and *RHBDF2* mutation, as have several of his family members that were previously published. Our objective was to determine the prevalence of esophageal cancer in this family, assess environmental factors and exposures, and evaluate screening practices and genetic counseling in these patients.

Surveys were mailed to 47 addresses with a response rate of 61.7%. The survey collected demographics and medical history (**Figure 1**). The survey asked about tylosis, mucosal irregularities, esophago-gastroduodenoscopy (EGD) surveillance, diagnosis of esophageal carcinoma, and genetic testing or counseling. Specific environmental risk factors were assessed including alcohol use, tobacco use, and exposure to well water.

Results

A total of 14/29 (48.3%) family members had a plantar keratoderma (**Table 1**). Five reported also having a palmar keratoderma. Of those with tylosis, 28.6% were female and 71.4% were male with an average age of 41 years. Two reported onset in childhood but the mean age of onset of tylosis was 15 years. In this family, 28.6% had associated oral leukoplakia and 21.4% of those affected individuals smoked, 64.3% reported drinking alcohol, and 28.6% reported drinking well water.

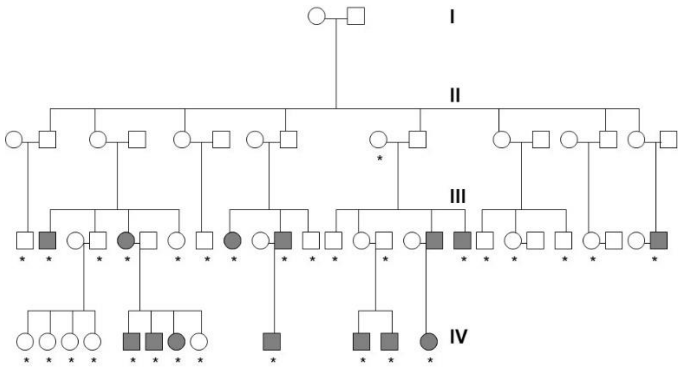

Figure 1. *Howel-Evans American pedigree. Gray shading indicates individuals with tylosis. The asterisk represents those family members that returned a survey.*

Table 1. *Characteristics of an American family with Howel-Evans syndrome.*

Characteristic	Tylosis (n=14)	No tylosis (n=15)
Sex		
Female	4	8
Male	10	7
Age of onset of tylosis		
Mean	15	N/A
Tobacco use		
Yes	3	1
No	11	14
Alcohol use		
Yes	9	10
No	5	5
Well-water use		
Yes	4	9
No	10	6
Oral involvement		
Yes	4	0
No	10	15
Esophageal cancer		
Yes	0	0
No	14	15

Over half of the affected family members (57.1%) never had an EGD performed. Those that received screening were receiving them at various intervals, ranging from annually to every 5 years. One started EGD surveillance at 20 years of age. None of these patients had yet been diagnosed with esophageal cancer; we suspect this relates to the younger average age of respondents. Several survey respondents wrote on the returned survey about deceased family members that had developed esophageal cancer. However, this information was not included in the data analysis. Despite the known mutation and autosomal dominant inheritance, only two reported that they or their children ever received genetic counseling.

One of the limitations to this study is that the mean age of our participants was 41 years, which is much younger than the reported age of onset of esophageal cancer in this family [4]. As noted in the pedigree, only one unaffected family member from generations I and II returned a survey. Given the inheritance condition of this disease, we hypothesize that some family members in these generations were affected with tylosis, leukoplakia, and esophageal carcinoma, but that data was unavailable through our available surveys of living participants.

Case Discussion

It is of particular importance that despite having this plantar keratoderma and a strong family history of esophageal cancer, less than half had ever had a screening EGD and only two had genetic testing or counseling. A prior study of this same family noted that seven of eight members with esophageal cancer were smokers [4]. Our study showed a low incidence of smoking from respondents and zero participants had been diagnosed with esophageal cancer, perhaps further demonstrating this association. It is also possible that since many of our participants had minimal to no screening, several of them could have undiagnosed esophageal cancers.

Conclusion

As dermatologists, we are on the frontline of diagnosing Howel-Evans syndrome and it is of utmost importance that we are familiar with this condition. When these patients come to us for treatment of their keratoderma, we must ensure that we counsel them regarding secondary risk factors such as smoking and alcohol use, refer for genetic counseling, and coordinate with their primary care physician to ensure appropriate screening EGDs are performed.

References

1. Howel-Evans W, McConnell RB, Clarke CA, Sheppard PM. Carcinoma of the oesophagus with keratosis palmaris et plantaris (tylosis): a study of two families. *Q J Med.* 1958;27(107):413-429. [PMID: 13579162].
2. Blaydon DC, Etheridge SL, Risk JM, Hennies HC, Gay LJ, Carroll R, et al. RHBDF2 mutations are associated with tylosis, a familial esophageal cancer syndrome. *Am J Hum Genet.* 2012;90(2):340-346. [PMID: 22265016].
3. Marger RS, Marger D. Carcinoma of the esophagus and tylosis: a lethal genetic combination. *Cancer.* 1993 (72):17-19. [PMID: 8508402].
4. Stevens HP, Kelsell DP, Bryant SP, Bishop DT, Spurr NK, Weissenbach J, et al. Linkage of an American pedigree with palmoplantar keratoderma and malignancy (palmoplantar ectodermal dysplasia type III) to 17q24. Literature survey and proposed updated classification of the keratodermas. *Arch Dermatol.* 1996;132(6):640-651. [PMID: 8651714].