A High Prevalence Rate of Tibia Hemimelia in a Subregion of West Azarbaijan, Iran

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Abstract

From 1995 to 2017 an abnormally high number of tibia hemimelia (TH) patients from the Maku subregion in the West Azarbaijan province of Iran were referred to our orthopedic department for treatment. Regarding the occurrence of TH in many families in a restricted region and negative results of available genetic tests, we hypothesized that a founder mutation etiology that is different from previous known genetic disorders might produce the trait of TH in our patients. Through a retrospective study, we collected demographic data including date of birth, patients and parents place of birth, sex, type of TH, presence of other musculoskeletal anomalies, and treatment from the patients who were referred to our department. We obtained a blood sample for genetic studies. We carried out genetic studies in cytogenetics and molecular levels on a patient with familial TH. The prevalence of TH in the Maku subregion of West Azarbaijan was 149.5 (95% confidence interval [CI]: 68.4–283.8) per 1 million live birth. The patients did not fit with any known syndromes with TH. Genetic evaluations of a patient with familial history of TH in this case series exhibited no detectable change in both cytogenetic and molecular levels. There was an obvious increased prevalence rate of TH in this province and particularly in the Maku subregion. The cytogenetic locations for known syndromic TH are not responsible for the observed anomalies in our patients. Our next step for detecting possible genetic mutations in our patients would be mutation analysis via very high-resolution whole genomic sequencing in more patients or genetic linkage study.

Keywords
- congenital anomaly
- genetic mutation
- tibia hemimelia

Introduction

Tibial deficiency or tibia hemimelia (TH) is a very rare congenital anomaly with an incidence of one in 1 million live births.[1] The Jones classification of TH includes type Ia, no tibia is seen on radiographs at term with no cartilaginous anlage; type Ib, no tibia is seen on radiographs at term but proximal tibial cartilaginous anlage exists; type II, proximal part of the tibia is ossified and present at birth but the distal part of the tibia is absent; type III, the distal part of the tibia is ossified and present at birth but the proximal part of the tibia is absent; and type IV, tibia is short and there is distal tibiofibular diastasis. Most of the TH patients are sporadic

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but some patients can be identified as an isolated genetic disorder or as a part of malformation syndromes.[1]

From 1995 to 2017 an abnormally high numbers of (TH) patients from Maku subregion in the West Azarbaijan province of Iran were referred to our orthopaedic department for treatments. This report presents the prevalence rate of TH in the West Azarbaijan province and in Maku subregion. Regarding the occurrence of TH in many families in a restricted region, we hypothesized that a founder mutation etiology which is different from previous known genetic disorders might produce the trait of TH in our patients.

Materials and Methods

In a retrospective manner, all the cases of TH that were referred to our department from 1995 to 2017 were identified. Epidemiologic characteristics including date of birth, patients and parents place of birth, sex, type of TH according to the Jones classification, presence of other musculoskeletal anomalies, and treatments were collected. The study was approved by research committee of the institute and with informed consent of patients and their parents; we also obtained a blood sample for genetic studies.

The number of live births in West Azarbaijan province and its subregions were obtained from the birth registration center and prevalence of TH was calculated for each subregion separately.

Using these prevalence rates, we produced a prevalence choropleth map for TH in this province during 1995 to 2017. Forming a maximum likelihood function, the odds ratio of each subregion was calculated.[2] The prevalence of TH in this period in the province entirely was selected as reference to calculate the ratios of each subregion during this time. Based on these ratios, we produced a hazard choropleth map for TH in the province and its subregions with ArcGIS10 software (Esri Products) to demonstrate the abnormal distribution of TH within the subregions of the West Azarbaijan province.

We carried out genetic studies in cytogenetics, molecular cytogenetics, and molecular genetics levels on a patient whose aunt was also affected with TH. In the cytogenetic level, high-resolution GTG banding karyotype with band resolution of 550 was performed on 20 metaphases. Since karyotype cannot rule out the possibility of microdeletions, microduplications, subtle chromosomal rearrangements, very low-level mosaicisms, and monogenic disorders; therefore, array comparative genomic hybridization (array-CGH [comparative genomic hybridization]) and whole genome sequencing (Centogene, Germany) were performed as molecular cytogenetics and molecular genetics tests, respectively.

Results

Based on the birth date of the patients from 1995 to 2017, 17 patients in West Azarbaijan province have been born with TH. Thirteen out of the 17 patients had the anomaly on the right side, while four patients had bilateral TH. There were 13 male and four female patients. Two patients were aunt and niece. Four patients had other anomalies in their upper and lower limbs such as cleft hand and polydactyly. There were 11 type IV, one type III, two type II, and seven type Ia of TH. All the patients had knee or below knee amputation and then fitted with prosthesis to improve their function (►**Figs. 1** and **2**).

Fig. 1 Clinical photo of 7-month-old boy with tibia hemimelia and severe foot and ankle deformity.

Between 1995 and 2017 the total occurrence of TH in whole West Azarbaijan province was 11.2 (95% confidence interval [CI]: 6.52–17.93) per 1 million live birth. Nine out of the 17 patients with TH were born in the Maku subregion. In the Maku subregion, the prevalence of TH was 149.5 (95% CI:

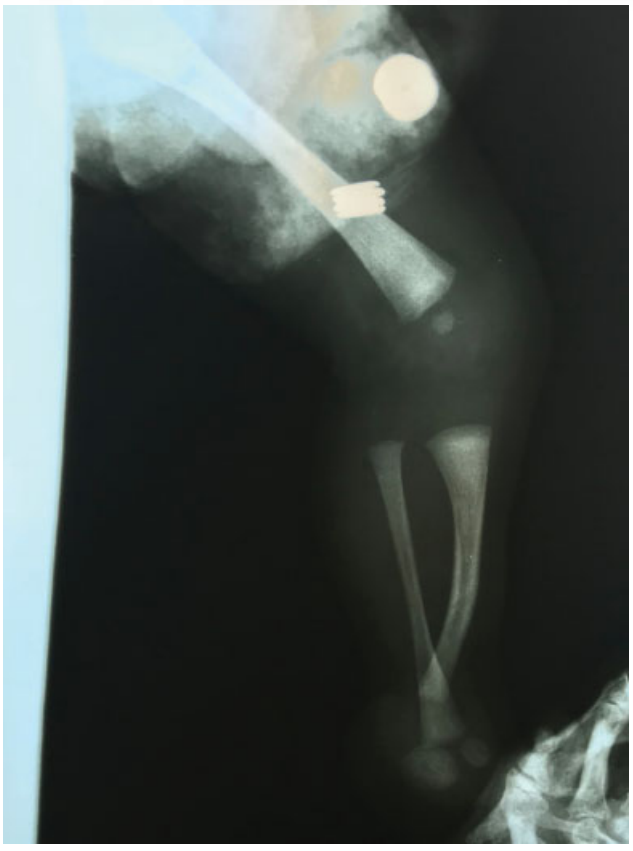

Fig. 2 Radiography of the patient with tibia hemimelia IV.

68.4–283.8) per 1 million live birth. Regarding the worldwide incidence of one in 1 million live births, the Maku subregion's figure was remarkably high. Meanwhile, two out of the eight remained patients that were born in the other subregions of West Azarbaijan had parents that were born in the Maku subregion. ►**Fig. 3** demonstrates the hazard choropleth map. ►**Fig. 4** demonstrates the prevalence choropleth map.

At the cytogenetic level, the karyotype of the examined patient was normal without any aberration. At the molecular cytogenetics level array-CGH and whole genome sequencing (Centogene, Germany) was normal without any pathologic or likely pathologic finding or even any variant with unknown significance (VUS).

Discussion

TH may have autosomal dominant or recessive inheritance patterns. Werner's syndrome (TH, pre- and postaxial polydactyly of fingers and toes, and triphalangeal thumbs), TH diplopodia syndrome, and TH micromelia–trigonobrachycephaly syndrome, and Nicolai–Hamel polysyndactyly syndrome (TH with polysyndactyly) are among syndromes with autosomal dominant patterns of inheritance. TH-split hand and foot syndrome and Gollop–Wolfgang complex (TH, ectrodactyly, hypoplastic radius, ulna, or femur) have autosomal dominant/autosomal recessive patterns of inheritance. Raas–Rothschild syndrome (TH, limb, and pelvis hypoplasia) and Acrorenal mandibular syndrome have autosomal recessive patterns of inheritance. According to Medgene, the known cytogenetic locations for TH are: 8q24.1, LMBRI (7q36.3) and two susceptibility loci at 1q42.2-q43 and 6q14.1 have been identified, leading to generate the hypothesis that this syndrome fits the model of digenic inheritance.

Deletion within the sonic hedgehog (SHH) repressor GLI3 has been reported in two patients with bilateral tibial hemimelia.[3] Laurin–Sandrow syndrome which is also

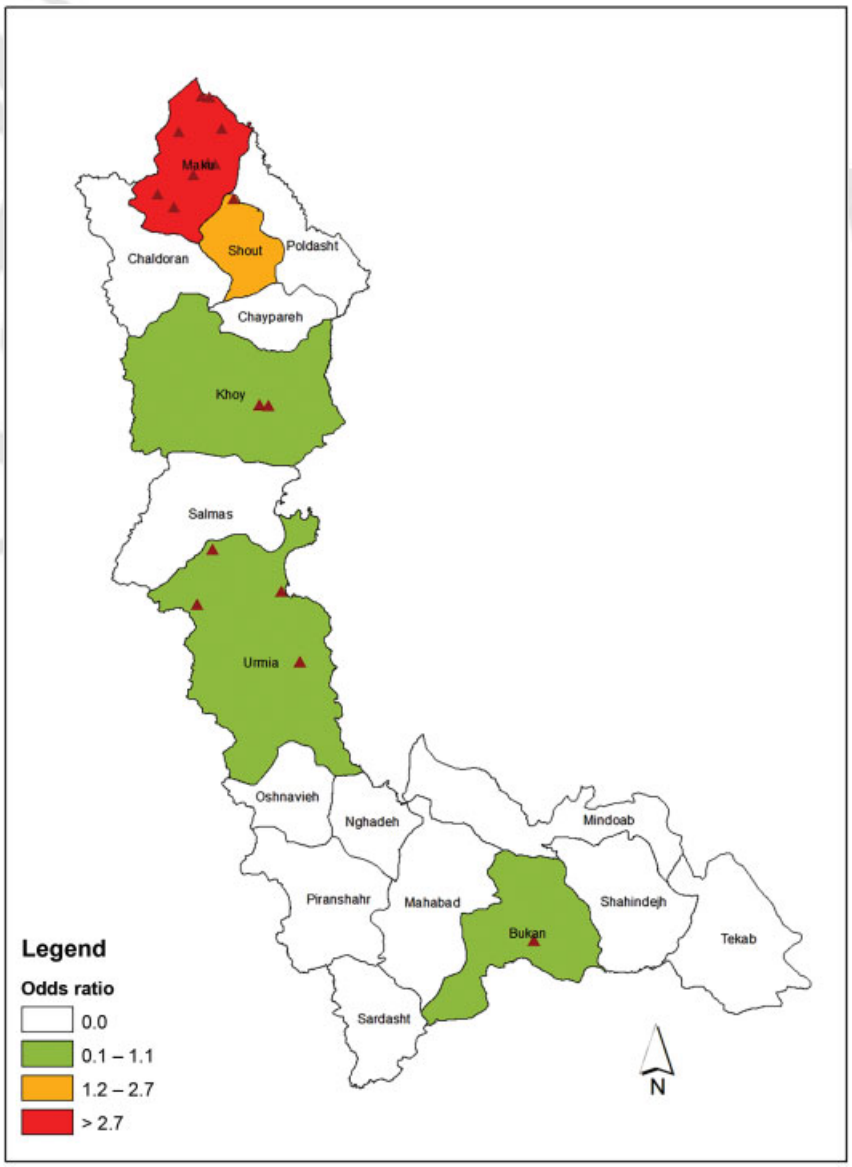

Fig. 3 The hazard choropleth map demonstrates the distribution of TH patients in the subregions of the West Azarbaijan province. TH, tibia hemimelia.

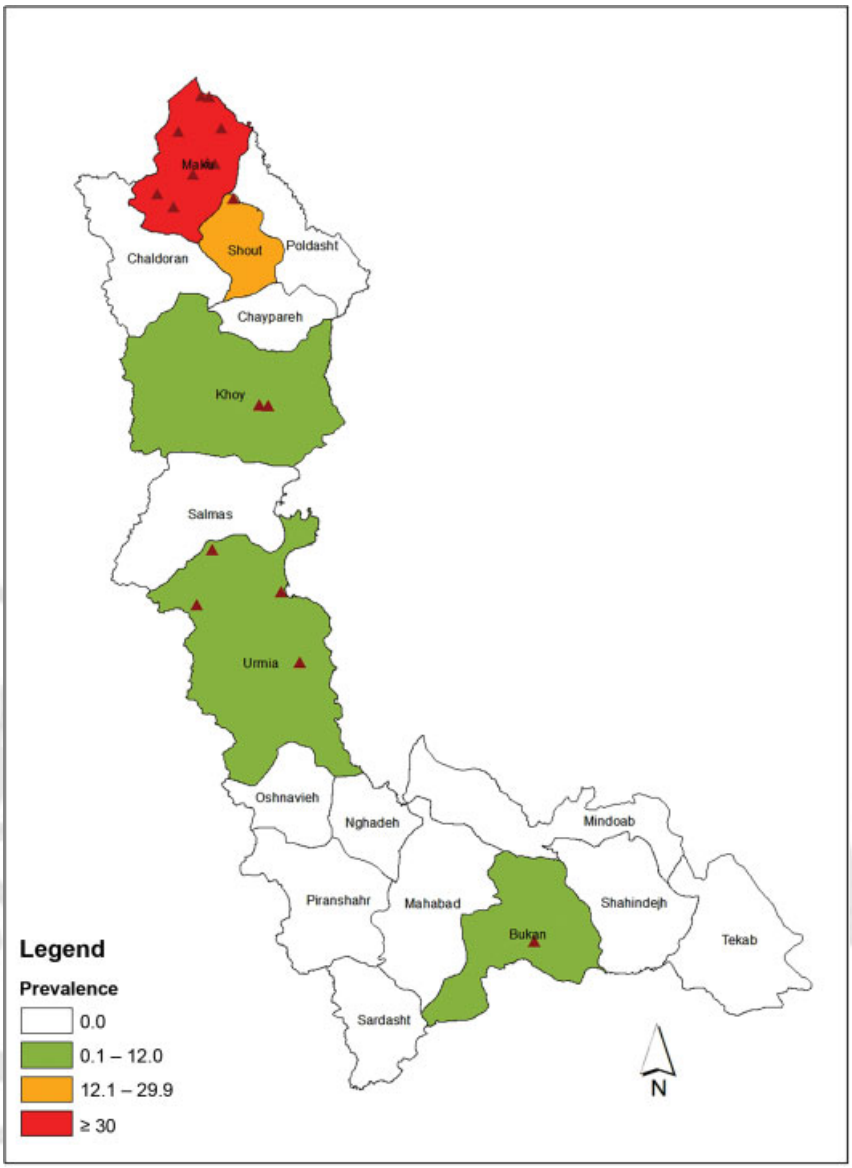

Fig. 4 The prevalence choropleth map demonstrates the distribution of TH patients in the subregions of the West Azarbaijan province. TH, tibia hemimelia.

associated with hypoplastic/absent tibia can be the result of 2p23.3;14q13 translocation.[4] Cytogenetic locations of Nicolai–Hamel polysyndactyly syndrome (TH with polysyndactyly) and split hand/split foot syndrome were mapped to 7q36.[5] and 10q24-q25[6] respectively.

The patients of the current study did not fit with any known syndromes with TH. Regarding TH as a developmental malformation and also the occurrence of repeated cases in many families, we strongly suggest that it has a genetic basis.

Regarding widespread prenatal ultrasonographic screening and terminating the pregnancies with major congenital anomaly such as TH, the chance of finding a new case of TH is negligible. Due to lack of necessary number of patients in a single family, it is impossible to reach a definite conclusion about pattern of inheritance; however, the pattern of inheritance in most of families seems to be autosomal dominant with incomplete penetrance. But in study of Chinnakkannan et al, the risk of TH has been higher in males than females. Also contrary to the findings of our study, the family history is usually negative.[7] One of the possible causes is the ethnic origin of people living in subregions of West Azarbaijan (Maku subregion). Familial and interethnic marriage is one of the most common traditions, and genetic mutations maybe occurring in other generations.

We intend to continue our study and our next step for detecting possible genetic mutations in our patients would be very high-resolution whole genomic sequencing in more patients or genetic linkage study, which is mapping a trait to a genomic location by demonstrating cosegregation of the disease with genetic markers of known chromosomal location. Towards this aim, we have obtained peripheral blood samples from our patients and also healthy family members and then stored the extracted DNA with standard protocol for future genetic studies. At the present step, we

are trying to gather more DNA samples, especially if possible, from families with the occurrence of TH in at least three generations, where reaching the aim will be more feasible.

This study had several limitations. TH is a rare disease so that our study was retrospective, and we are unable to design the prospective study and perinatology evaluation. A careful review of the genealogy and inability to analyze the gene mutation for the probability occurring is the limitations of study.

Conflict of Interest

This manuscript is based on a doctoral thesis with the registered number 1396-09-63-2865 at Urmia University of Medical Sciences. There is no conflict of interest in preparing this manuscript.

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