Journal of Pediatric Urology (2016) 12, 307.e1—307.e5

Altitude as a risk factor for the development of hypospadias. Geographical cluster distribution analysis in South America

Nicolas Fernández [a], Armando Lorenzo [b], Darius Bägli [b], Ignacio Zarante [a]

[a]Pontificia Universidad Javeriana, Bogota, Colombia

[b]Division of Urology, Hospital for Sick Children and University of Toronto, Toronto

Correspondence to: N. Fernández, Pontificia Universidad Javeriana, Carrera 7 No 40 — 62, Hospital Universitario San Ignacio, Octavo piso, Bogota, Colombia

Fernandez.j@javeriana.edu.co (N. Fernández)

Keywords
Hypospadias; Prevalence; Geographic clusters; Spatial analysis; ECLAMC

Received 19 October 2015
Accepted 12 March 2016
Available online 22 April 2016

Summary

Objective
Hypospadias is the most common congenital anomaly affecting the genitals. It has been established as a multifactorial disease with increasing prevalence. Many risk factors have been identified such as prematurity, birth weight, mother's age, and exposure to endocrine disruptors. In recent decades multiple authors using surveillance systems have described an increase in prevalence of hypospadias, but most of the published literature comes from developed countries in Europe and North America and few of the published studies have involved cluster analysis. Few large-scale studies have been performed addressing the effect of altitude and other geographical aspects on the development of hypospadias. Acknowledging this limitation, we present novel results of a multinational spatial scan statistical analysis over a 30-year period in South America and an altitude analysis of hypospadias distribution on a continent level.

Method
A retrospective review was performed of the Latin American collaborative study of congenital malformations (ECLAMC). A total of 4,020,384 newborns was surveyed between 1982 and December 2011 in all participating centers. We selected all patients with hypospadias. All degrees of clinical severity were included in the analysis. Each participating center was geographically identified with its coordinates and altitude above sea level. A spatial scan statistical analysis was performed using Kulldorf's methodology and a prevalence trend analysis over time in centers below and above 2000 m.

Results
During the study period we found 159 hospitals in six different countries (Colombia, Bolivia, Brazil, Argentina, Chile, and Uruguay) with 4,537 cases of hypospadias and a global prevalence rate of 11.3/10,000 newborns. Trend analysis showed that centers below 2000 m had an increasing trend with an average of 10/10,000 newborns as opposed to those centers above 2000 m that showed a reducing trend with an average prevalence of 7.8 ($p = 0.1246$). We identified clusters with significant increases of prevalence in five centers along the coast at an average altitude of 219.8 m above sea level ($p > 0.0000$). Reduction in prevalence was found in clusters located in two centers on the Andes mountains. Altitude of 2,000 m was associated with hypospadias (Figure), with an OR 0.59 (0.5—0.69). There are ethnic arguments to support our results supported by protective polymorphism distribution in high lands.

Conclusion
Altitude above 2,000 m is suggested to have a protective effect for hypospadias. Specific clusters have been identified with increased risk for hypospadias. Environmental risk factors in these areas need to be further studied given the association seen between altitude and the distribution of more severe cases.

Figure Spatial-temporal analysis. Identified hypospadias clusters with increasing trends in prevalence (red) and clusters with decreasing trends (blue).

http://dx.doi.org/10.1016/j.jpurol.2016.03.015

Introduction

Birth defects are the most common cause of morbidity and mortality among infants around the world [1]. Surveillance systems allow a better understanding of the etiology of congenital anomalies, identification of prevalence estimates and trends, and planning and implementation of preventive measures in public health [2]. Some epidemiologic measures such as geographical cluster identification, defined by the EUROCAT as an unusual aggregation of cases in a period of time, and prevalence trend analysis have been shown to be good approaches and techniques in public health systems for studying congenital anomalies [3]. In recent decades multiple authors using surveillance systems have described an increase in prevalence of hypospadias, but most of published literature comes from developed countries in Europe and North America and few have performed cluster analysis [3–6]. Results from these studies have identified associated risk factors in the development of hypospadias, such as birth weight, mother's age at gestation, exposure to endocrine disruptors, and *in vitro* fertilization [7,8].

Nonetheless, not much is known about the effect of altitude on the development of hypospadias. As stated by Castilla et al., altitude might be a risk factor for some congenital anomalies such as craniofacial defects, but protective for others such as hypospadias and neural tube defects [9]. As just mentioned and given the effect of the environment in the development of hypospadias, we believe that geographical and long-term prevalence trend analysis is key to better understand the behavior of hypospadias in our region [10]. Hereby we present novel results of a multinational spatial scan statistical analysis over a 30-year period in South America and an altitude analysis of hypospadias distribution on a continent level.

Method

The Latin American collaborative study of congenital malformations (ECLAMC) is a multicenter project designed to identify associated risk factors in the development of congenital anomalies [11]. For the purpose of the present study we used the ECLAMC methodology and database to analyze our results.

Data collection is performed daily in each participating center in a standardized manner. Every day, all of the newborns are evaluated looking for congenital anomalies. Parents are interviewed and newborns examined by trained personnel. Data are registered by each participating center and sent to the ECLAMC headquarters monthly.

As the ECLAMC is a case-control model, for each patient with a detected congenital anomaly a control is included. Controls are the immediate next newborn, of the same sex as the case. Information gathered for controls is exactly the same as that for cases. For the present study we did not include controls in the analysis. Before each participating center is included in the study it must be accepted by the local investigational review board (IRB).

For the present study we reviewed retrospectively the ECLAMC database from January 1982 to December 2011. Analyzed data included all registered patients diagnosed with hypospadias during the study period. Prevalence was calculated in all hospital newborns registered during the study period. A clinical severity classification was used following Duckett's description (Glanular, Coronal, Penile and Scrotal) [12,13].

We excluded information from centers that did not have a continuous follow-up (periods of more than 5 years without surveillance and data collection) or that had more than 40% of the collected data incomplete. During the study period, 192 centers in 11 countries supplied data. After excluding countries with incomplete information, a final analysis was done in 159 hospitals from six South American countries.

For the altitude variable analysis we used all centers and compared registered prevalences according to clinical severity separating results in two groups, those above and below 2,000 m, as suggested by other authors [9]. Prevalence trend analysis was estimated using a Cochrane Armitage analysis. Registered range of altitude was from 1 to 3,700 m above sea level. Comparison was done using odds ratios (OR) and calculated with the software EpiCalc 2000 version 1.02. The OR and 95% confidence intervals were used to estimate the relative risk [14]. A comparison of prevalence trend over study period was performed between centers above and below 2,000 m and significance was analyzed using a t test.

Geographical variables as potential risk factors were evaluated for each center using registered coordinates as well as altitude above sea level. We used this information following spatial scan statistical analysis under a Poisson model given the size and diversity of the results [15]. The aim was to determine geographical areas with either high or low prevalence rates over time by comparing expected cases with detected cases. The p value for significant differences in prevalence was obtained by the Monte Carlo model of 999 replications and was set up at $p < 0.05$. A multinominal prevalence rate logistic regression was performed using geographic areas as the outcome to establish significant differences between clusters. Identical coordinates were combined into one location. Excluded identified clusters were the ones with no statistically significant results or those where the increase or decrease was identified in a single center. The only restrictions we made before running the data were that the number of captured newborns in a given area did not exceed 10% to reduce overlapping clusters. This change was done to limit overlapping centers with no impact on the significance and power of the results [16]. Results were set up to be translated to Google EarthTM for graphical visual results. This same analysis was then performed selecting cases by clinical severity (glanular, coronal, penile, and scrotal cases).

Results

Between January 1982 and December 2011, participating centers conducted surveillance on 4,020,384 newborns, detecting a total of 4,537 hypospadias cases, and resulting in total prevalence of 11.3 per 10,000 newborns. Trend analysis showed that centers below 2,000 m had an increasing trend with an average trend of 14.9 per 10,000 newborns as opposed to those centers above 2,000 m that