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Indian Journal of Medical Sciences

Original Article

Genetic epidemiology of rare diseases in San Luis Province, Argentine

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ABSTRACT

Objectives: Genetic epidemiologic studies in populations of the world are scarce and this medical information is of special value for clinical geneticists. The purpose of this work was to know and to implicate the geographical environments with the genetic diseases found in patients attending a genetic consulter, according to the type of work, place of residence, or environment characteristic in the province of San Luis, Argentine.

Material and Methods: Clinical genetics consultations during 2014–January 2019 were analyzed for all patients derived to the primary consultation center, and nearby hospitals in San Luis. A total of 448 patients were registered and examined once a week at the Central Hospital of San Luis. The reasons of the derivate medical consultations were divided into major malformations (MMal), neurodevelopment diseases, and genetic counseling. In addition, possible environmental risk factors such as urban or rural origin, the working activity of parents in manufacturing houses or mines, and drug consumption during pregnancy were also considered. The prevalence of genetic diseases was calculated for all eight province departments and compared with the province's apparent prevalence.

Results: In the whole sample (n = 448), the major proportion of patients came from the city. Patients with MMals were the most abundant and significantly higher than the other categories. The prevalence of MMals distributed approximately similarly in all departments of the province, with exception of two of them. No association was found between types of work or drug abuse with MMals in this sample.

Conclusion: Of all types of genetic diseases, the most prevalent was the MMals. Regarding its prevalence, except for two departments, each department's prevalence had a similar distribution. Most of the affected patients with this type of genetic condition were found in the city and not in other regions of supposed risk.

Keywords: Rare diseases, Major malformations, Environment, Teratogens

INTRODUCTION

Genetic epidemiology studies the prevalence of different diseases on a genetics basis in human populations, regarding whenever possible, the relationships between the genotype and environment that may provoke diseases in the human being.[1]

This is the base for considering its applications and analysis as an important tool for the prevention and control of diseases with genetic backgrounds.[1] With the advance in technology and knowledge about gene actions, this discipline investigates the consequences on the health of the genetic variants.[2] Knowledge in genomics acquired in the past two decades has shown that the traditional category of genetic diseases includes only those where the contribution of genes is important, when in fact, genetic diseases cover a long spectrum of alterations reflecting the distinct contribution of environment and genes. Under this perspective, there exists limited information about the influence of the environment on genetic diseases in the different populations in the world. San Luis is a province located South-east of the New Cuyo Region of Argentine, and it is politically divided into eight departments with varied geographic characteristics. It is possible to think that theoretically, these varied geographical features could influence gene expression leading to some genetic diseases. This possibility has not been studied previously in San Luis, and the present observational study is to be expected to cover the actual scarce knowledge available.

Argentina has a National Network of Congenic Anomalies (RENAC-Ar, in Spanish) which provides year by year a register of the major congenic anomalies in newborns. However, these valuable data do not always satisfy all doubts in the medical genetic consultations, because the information is restricted only to the pediatric population as the primary server, disregarding anomalies present in young or adult patients attending the genetic consultation. On the other hand, the register does not take into account the environmental factors

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Received: 16 February 2021 **Accepted:** 21 September 2022 **EPub Ahead of Print:** 05 December 2022 **Published:** 02 January 2023 **DOI**: 10.25259/IJMS_67_2021

present in the different regions of the country which might explain the local gene-environment interaction.[3]

Considering this background, the purpose of the present report was to describe our experience in the genetic medical attention of patients attending the Central Hospital of San Luis, where the possible relevance of the environment to the genetic condition of patients was studied.

MATERIAL AND METHODS

Population of the study

All patients attending to an external genetic consulter, derived from other medical specialties, including those sent by internal consultations from 2014 up to January 2019 with a frequency of attention of once a week, were considered the target population. By definition, the sample (n = 448) was biased in addition to being an open investigation where the cutoff point was arbitrarily chosen.

Type of study and experimental design

In the initial phase, the investigation was descriptive. In its second phase, prevalence and when was appropriate, its possible relationship with clinically relevant potential risk factors was studied.

Statistical analysis

The analysis of the significance of the differences between prevalence was made with the χ^2 Distribution. Probability <0.05 was considered statistically significant.

Variables and categories

Variables analyzed were:
1. Major congenital anomalies evaluated as proportions
2. Neurodevelopment diseases (NeurD), evaluated as proportions
3. Genetic counseling (GAsess), evaluated as proportions.

Description of the field of study

The field of study was the external genetic consultations at the Policlínico Central de San Luis, where patients from all parts of the province of San Luis are derived, and also included the interconsultations of patients interned in the same hospital and Teresita Baigorra (San Luis) or Villa Mercedes Juán Domingo Perón hospitals.

RESULTS

The total of 448 patients according to the latest province survey represents 0.09% of the total province population. Due to the low number of patients analyzed, it was considered prudent to calculate the *Apparent Province Prevalence* of the total genetic anomalies ($P_{appProv} = 6.6 \times 10^4$ inhabitants), which was used to compare with each of the departments' prevalence considering the region of origin of patients in all the categories analyzed.

[Figure 1] shows the distribution of all patients categorized as "Living in the city" (LCity) and "Non-living in the city," that is, those patients who declared a site of work and/or living place in the city of San Luis, and all those coming from other departments or distant towns. The major proportion of patients coming from the city of San Luis was significantly different from the proportions of patients coming from other places [Figure 1, $P << 0.01$].

[Figure 2] shows the distribution of medical consultations categorized into three groups: "Major malformations" (MMal), "NeurD," and "GAsess," covering the major amount of all attended patients. In other categories, the number of subjects was very low to consider a statistical analysis. As shown in [Figure 2], the proportion of patients with "MMals" was statistically higher than the other categories ($P <<< 0.001$) reaching 78.4%.

[Figure 3] shows the apparent prevalence of MMals from the different departments compared to the apparent province prevalence. As shown, only two departments showed a significantly lower prevalence than the $P_{appProv}$ (Pedernera and Junín departments, $P <<< 0.001$).

[Figure 4] shows the proportion of the MMals in the province of San Luis, according to work activity or exposition to drugs of abuse. As shown, the highest proportion of affected patients was found in those people working, or living in the city, statistically different from all the rest of the working activity or exposed groups ($P <<< 0.001$).

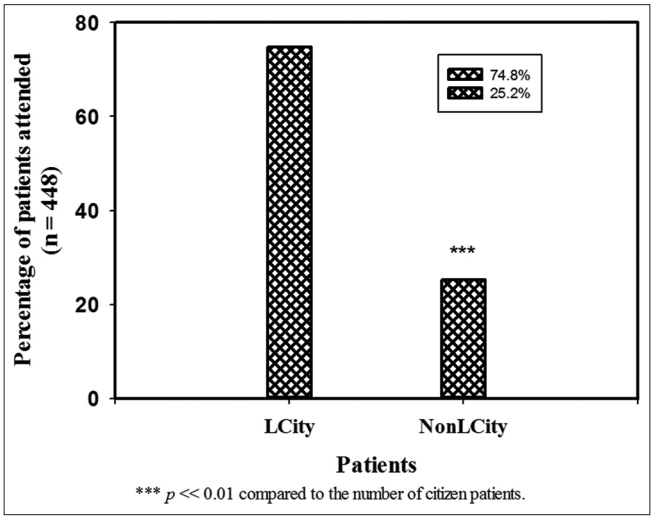

Figure 1: Proportion of patients attended in the province of San Luis according to the site of work or living. LCity: People living in the city of San Luis. NLCity: People not living in the city of San Luis ***P.

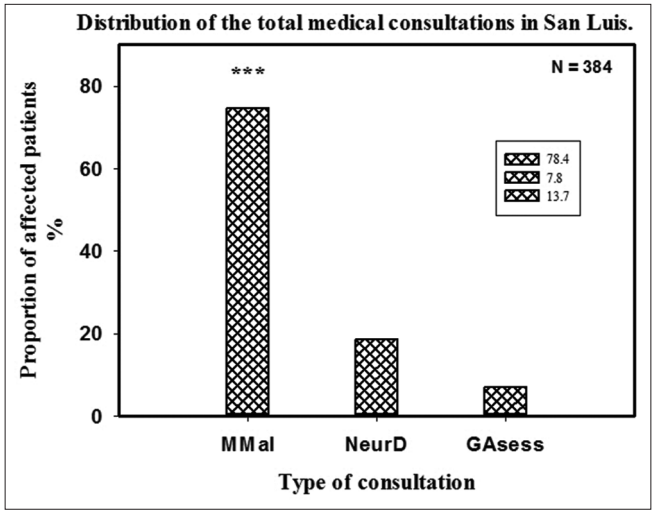

Figure 2: Distribution of all genetic consultations performed in San Luis in the period studied. MMal: Major malformations, NeurD: Neurological diseases, GAsess: Genetic counseling consultations ***P.

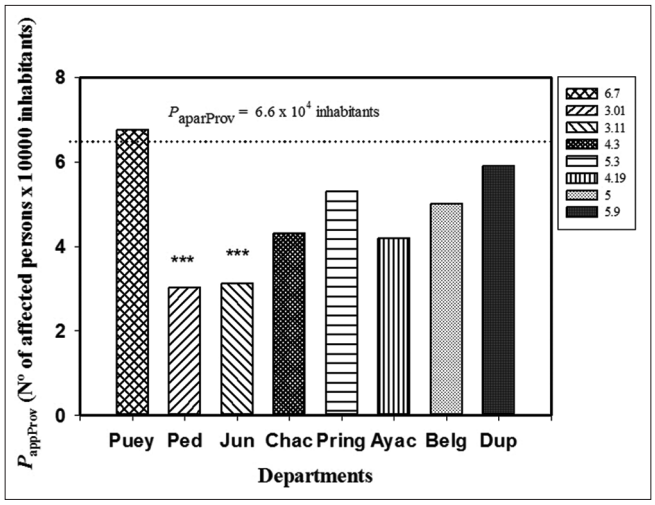

Figure 3: The prevalence of major malformations in the different departments of San Luis province compared to the overall apparent province prevalence. PappProv: Apparent province prevalence, Puey: Pueyrredón, Ped: Pedernera, Jun: Junín, Chac: Chacabuco, Pring: Pringles, Ayac: Ayacucho, Belg: Belgrano, Dup: Dupuy ***P.

DISCUSSION

As previously mentioned sampling was biased and certainly did not strictly represent an accurate scope of genetic epidemiology in the San Luis Province population. Patients traditionally visit a genetic consulter derived by other physicians. It is reasonable to consider that the real amount of patients is higher than the actual attended by the genetic consulter. This picture can be explained by several reasons. One of them is the lack of communication in the public health system. Other refers to the common practice of the

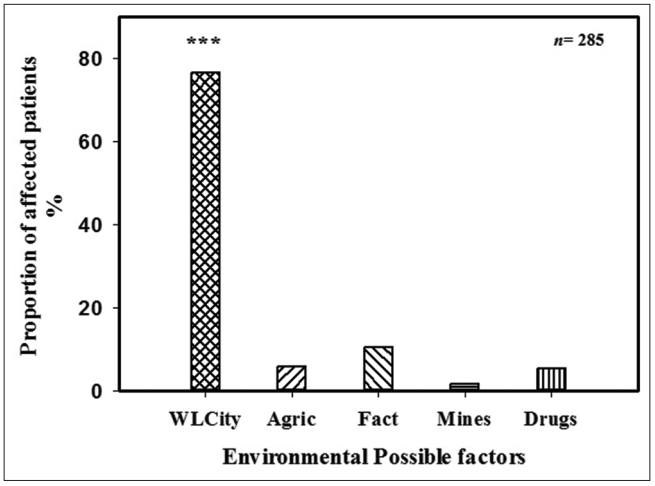

Figure 4: Distribution of the Major Malformations in San Luis Province, according to the working activity or previous exposition of drugs of abuse in the total of 285 patients examined in the period studied. The environmental conditions of working activity or exposition to drugs were considered as possible environmental factors influencing the genetic conditions. WLCity: People working or living in the city, Agric: People working in agriculture, Fact: People working in mines, Drugs: People exposed to drugs of abuse during pregnancy ***P.

"well-known and obvious phenotype." This is the case of children with Down syndrome when the non-geneticist professional does not consider the need to derivate or solicit a confirmatory karyotype examination. Other is non-nearness to the attention consulter. In small towns away from the capital, the factor of distance to reach the weekly consultation in the capital put additional problems, since it is frequent the need to authorize genetic studies, solicit attention turns, or transport disabled patients that require additional time to fulfill the need to consultation. Perhaps, this can explain why a great number of patients was found in those LCity compared to those living in the periphery zones [Figure 1]. In addition, economic and social factors could have influenced the reduced proportion of people living outside the capital to attend the consulter.

It is evident from [Figure 2] that "MMal" was the genetic disorder most frequent in all the genetic consultations in the San Luis Province. This is not an unexpected result since this type of genetic disorder calls immediately the attention of parents and their urgent consultation with the geneticist. The apparent prevalence of each department for this genetic disorder with two exceptions was in concordance with the apparent province prevalence [Figure 3]. Regarding the unexpected low apparent prevalence found in the department of Pedernera, it is possible to explain it, considering that this is the region where the second most important maternity hospital in the province is located. The medical staff tends to resolve diagnostics and derivation to hospitals outside

the province of San Luis. Concerning the Junín department located northeast of the San Luis Province, patients prefer to attend the nearby hospitals of the province of Cordoba (another nearby province). This would explain the low count of cases observed in these two departments of San Luis province [Figure 3].

Regarding the NeurD, which represented about 18% of all consultations [Figure 2], some peculiar characteristics might explain this low observed percentage. The NeurD represents a complex compromise to healthcare. They have in common lacks in personal, social, academic, and deficient working functioning,[4] because they are a heterogeneous sickness, complicating the correct diagnosis. Patients might show slowness in the acquisition of maturing patterns, mental retardation, autism, and other signs that can be present also in MMals, such as the case of the Rett or Asperger syndrome.[5]

In this work, patients showing a deficit in the acquisition of development patterns and/or behavioral alterations were allocated in this category.

Regarding the NeurD [Figure 2], particular interest has been paid to know the possible causes underlying their origin. In these later years, workers have advanced the idea that neurotoxicity might be the cause of the alterations in neurodevelopment.[6] However, the complexity of the disease compels us to take into account other considerations. It is clear that the major amount of clinical signs does not belong to well-known genetic diseases. In the *Online Mendelian Inheritance in Man*, the keyword *mental retardation* shows 3400 mentions, while the keyword of *autism* shows only 567 mentions. Obviously, in these entries mental retardation and/or behavioral disruption, signs have been included since these characteristics are part of a syndrome ensemble of many other diseases. However, many times this is not true, and signs such as behavioral disruptions or mental retardation in particular patients, can be explained by considering that many genes by mutation, or increased genic susceptibility may be part of the etiology. Furthermore, the parent's genetic antecedents are not mentioned depriving this important information to the clinic geneticist. Toxicity is invariably linked to the environment. Environmental factors are a reasonable explanation for the increase in neurodevelopment alterations. However, the most common interpretation has been to think of toxic compounds acting during critical periods of fetal development.[6]

Few explanations, mostly hypothetical, are claimed about mechanisms linking gene interaction with environmental factors.[7] It is interesting to consider that an environmental factor can be an important agent to modify genetic mechanisms but not necessarily by a toxic action. In our laboratory, we have found that certain environmental inorganic agents can epigenetically modify the methylation pattern of DNA in children changing the genetic expression and giving phenotypic modifications.[8,9] This evidence was obtained in school children of La Rioja Province, Argentine,[10] and later supporting evidence from animal studies was found with tellurium, one of the inorganic elements found in high concentrations but not at toxic levels in soil and water of mountain and mineral deposits region in La Rioja Province.[11] Thus, the influence of environmental agents can be subtler regarding changes and their following modified phenotypic expression.

Finally, as shown in [Figure 4], intent to implicate the various environmental sites involved in the type of work, living or drug abuse to genetic disorders in the period studied in San Luis, the highest proportion in the MMals was found in those patients living and working in the city [Figure 4]. Neither working in rural regions (agriculture), factories, or mines nor drug abuse was found to be related to MMals, and its proportions were very low [Figure 4]. Perhaps, the small size of a sample of patients fulfilling the characteristics selected did not put into evidence if any of these factors could be exerting a definitive role. Some other studies have been published with a similar approach to the present work but focalized on watchfulness and not addressing the social environment relationship.[10,12-19]

CONCLUSION

Even the amount of studied patients in the present report is low for a full significance to an epidemiologic approach, the great diversity of sickness which motivated the consultation put into evidence the need to continue in this line of work focusing on the environment-disease relationship which strengthens knowledge of disease processes, more selective treatments, directed prevention decisions, and efficient health strategies. It is worthwhile to comment that a prevailing concept in Medical Genetics is that possible environmental insults to patients should be tackled collaterally to a problem of teratogenic influence. Perhaps, a more enlightened approach should be taken into consideration that "environment" is a more dynamic and wide notion considering the General Theory of Systems as proposed some time ago by von Bertalanaffy.[20] Thus, the genome may be viewed as a system in interaction with the cytoplasmic compartment and the subsequent external compartments surrounding cells and the whole individual.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Ratti SG, Barroso R, Alvarez EO. Genetic epidemiology of rare diseases in San Luis Province, Argentine. Indian J Med Sci 2022;74:134-8.