Original Article

High prevalence of congenital hypothyroidism in Isfahan: Do familial components have a role?

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Abstract

Background: Despite elimination of iodine deficiency, the rates of both permanent and transient congenital hypothyroidism (CH) in our study were higher than the comparable worldwide rates, which emphasize the major role of genetic factors in the pathogenesis of CH and many studies in this regard confirm this possibility.

Materials and Methods: In this review, we report all studies that established during CH screening program regarding familial and genetic component of the disease.

Results: Although we could not entirely ignore the possible role of environmental and autoimmune factors in the development and function of thyroid gland, our findings strongly suggest the role of genetic factors as dominant etiologic factor in CH.

Conclusion: The studies support the existence of a familial component of CH involving dominant genetic predisposition factors with a low penetrance. Considering the polygenic/multifactorial basis of CH, they suggest the possible involvement of other unknown genes in the pathogenesis of the disease, which may also follow non-Mendelian pattern of inheritance.

Key words: Congenital hypothyroidism familial, dysgenesis, dyshormonogenesis, genetic

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INTRODUCTION

Congenital hypothyroidism (CH) with a rate of 1 in 3000 to 4000 live births is considered as the most common endocrine disease.[1,2]

CH is the most preventable cause of mental retardation in children, so, CH screening worldwide has been practiced widely to detect and treat CH patients.[3,4] CH screening history dates back to 1974 when it was established as a pilot screening program in Quebec, Canada, Pittsburgh and Pennsylvania, USA.[5] Thereafter, it developed in many developed countries and is underdeveloped in many developing countries, including Iran.[6] It was established in Iran for the first time in 1997 by Azizi *et al.* After that it was established in Shiraz province by Karamizadeh *et al.* who reported a prevalence of 1/1433 live births. Following elimination of iodine deficiency, it is re-established in Tehran and Isfahan by different screening methods, but both of them have reported an overall high prevalence of CH in studied regions (1/370 in Isfahan

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and 1/914).[7-9] Since then, the nationwide CH screening program was established in 2005, in Iran. The results of the nationwide CH screening program have also indicated the high prevalence of CH in Iran.[10]

Considering the high prevalence of CH in Isfahan, many studies have been performed in contemporary with CH screening program in Isfahan to investigate the etiology of CH in our region to better eradication of CH-related mental retardation and other complications.

CH considered as a multifactorial disease and many genetic, environmental, and autoimmune factors contributes in its pathogenesis.[11-13] Studies regarding the role of autoimmune factors have indicated that it had no significant role in the pathogenesis of CH, in this population.[14] From environmental factors, the role of iodine deficiency or excess was investigated. Iodine deficiency had no significant role in this regard.[15]

The finding of CH screening in Isfahan was not similar to the results of other studies worldwide. The etiology of CH was different from that reported in many other studies. The most common etiology of CH was dyshormonogenesis.[16] Female-to-male ratio was not similar to other studies in this field, which showed female predominance. Despite elimination of iodine deficiency, the rates of both permanent and transient CH in our study were higher than the comparable worldwide rates.[16] These findings emphasize the major role of genetic factors in the pathogenesis of CH and many studies in this regard confirm this possibility. In this review, we report all studies that established during CH screening program regarding familial and genetic component of the disease.

However, it is very important that in accordance with appropriate nationwide CH screening program to diagnose and timely treatment of CH patients, we have an opportunity to use achieved data during this screening program to perform researches in the pathogenesis of CH in our community.

REVIEW

Etiology of congenital hypothyroidism

The most common cause of CH worldwide is iodine deficiency, but in areas with adequate environmental iodine, CH commonly results from a spectrum of thyroid gland developmental defects, thyroid dysgenesis (TD), which is responsible for 85% of CH patients and includes thyroid agenesis, ectopic thyroid tissue, thyroid hypoplasia, and thyroid hemiagenesis. In the remaining 15%, CH results from thyroid dyshormonogenesis, with defects in one of the multiple steps required for normal hormone synthesis.[17-19]

TD is usually regarded as sporadic with a female predominance, but recent studies estimated that higher rate of familial cases of TD, affirming the existence of a strong familial component in CH due to TD. Evidences suggest that mutations in transcription factors, such as TTF2, TTF1, and PAX-8 and TSH receptor gene could be responsible for TD.[20-24]

Thyroid dyshormonogenesis is typically recessive and more commonly seen in inbred families and a wide spectrum of mutations in NIS (natrium-iodide symporter), pendrine, thyreoglobulin (TG), thyroid peroxidase (TPO), and THOX-2 genes have been identified in this field.[25-30]

Congenital hypothyroidism and consanguinity

Considering the high prevalence of parental consanguinity in our community, it seems that high rate of CH in our population is due to this factor, as reported by many studies previously.[31,32] However, a few studies have shown no significant relationship between consanguinity and CH.[33]

Many studies in Asian and non-Asian countries have indicated that CH is more prevalent in Asian families because of the parental consanguinity.[34-37]

Ordookhani and colleagues have shown high prevalence of parental consanguinity among cases of CH in Tehran.[38] We also reported a higher prevalence of familial marriage among parents of CH patients, especially first-degree relative consanguinity, in Isfahan.[39] But our results and the results of Ordookhani *et al.* have indicated a high rate of consanguinity among CH patients with TD. Parental consanguinity was present in 55.6% of dysgenetic, 42.9% of dyshormonogenetic, and overall 28.6% of 23,227 screened infants in Tehran. Odds ratio of consanguinity in permanent CH and dysgenesis was 2.75 (1.17–6.47) and 3.74 (1.33–10.52), respectively.[38] In Isfahan it was more prevalent in ectopic and dysgenetic CH patients than dyshormonogenetic ones.[39] Whereas regarding the autosomal recessive inheritance form of thyroid dyshormonogenes, which is also the common etiology of CH in Isfahan, we are looking for high rate of familial marriage among dyshormonogenetic CH patients. Therefore, the findings mentioned here warranted more studies for determining the genetic basis of CH in this region.

CH and thyroidal and extrathyroidal congenital malformations

Many studies have revealed that CH is associated

with a higher rate of both thyroidal and extrathyroidal congenital malformations, from which the majority were cardiac ones.[40-43] There are some evidences that gene mutations responsible for CH and defects in thyroid organogenesis, could also cause different developmental abnormalities.[44,45] Van Vliet have reported that mutations in TTF-1, TTF-2, PAX8, and TSHR are found in <10% of patients with CH and these patients have orthotopic thyroid hypoplasia in most of the cases and commonly associated with other malformations.[46]

Sabri *et al.* in Isfahan have investigated the prevalence of congenital cardiac malformations in congenital hypothyroid patients and according to their results cardiac malformations were present in 30.2% and 15.2% of case and control groups, respectively; that is, a higher prevalence in CH patients than in controls. They concluded that, although many pathophysiological mechanisms may be involved in cardiac malformations in CH patients, the involvement of genetic factors in the pathogenesis of CH seems more prominent.[47]

Evidences indicate that among first-degree relatives of a CH population with TD, there is an elevated rate of asymptomatic thyroid developmental anomalies when they are systematically screened for by ultrasound.[43] It is reported that thyroid gland abnormalities (nondevelopmental), such as goiter is also more frequent among mothers of infants with CH.[48] So it seems possible that a common underlying mechanism exists for both etiologic groups.[49]

In this regard, Adibi and colleagues have studied the prevalence of thyroid abnormalities among first-degree relatives of children with CH by ultrasonography. They indicated that the frequency of thyroid gland developmental abnormalities were higher among parents and siblings of CH patients than normal population. Thyroid developmental abnormalities were present among 3.5% of parents of CH patients and 10.5% of their siblings, whereas there were no thyroidal developmental abnormalities among the control group. Seventy-five percent of their reported thyroid developmental abnormalities were thyroid hemiagenesia, which is a rare form of TD, which can occur as a familial disorder, associated with any form of TD.[50] Most subjects with this abnormality may present with subclinical hypothyroidism.[51] Our observations, in accordance with the studies.[43,49,52] in this field, support the hypothesis of genetic component of TD, and suggest an association between asymptomatic hemiagenesis and TD. The results confirm previous genetic hypothesis and provide insights for further genetic studies in this field. The results of this study revealed that the frequency of TD is relatively high among relatives of CH patients in Isfahan. It also supports previous hypothesis that there are common sources for defects in embryogenesis, migration, differentiation, and growth of the thyroid gland during organogenesis. Consequently, these defects could either lead to TD among CH patients or those with asymptomatic TD.[53]

Baris *et al.* have indicated that thyroid gland could develop even in the presence of TTF-2 gene mutation and this mutation may be seen in syndromic CH patients without total thyroid agenesis.[54]

In line with other studies, our findings have strongly suggested an early impairment in the initial phase of embryo development, which consequently involves different organs.

Following the study of Adibi *et al.* and other studies performed in this field, as a complementary study to clarify the role of familial and genetic factors in the etiology of CH, Hashemipour and colleagues studied thyroid function abnormalities among first-degree relatives of CH patients in Isfahan. Their results showed that thyroid function abnormality, especially hypothyroidism, was more frequent among first-degree relatives of CH patients than in the control group.[14]

Karakoc *et al.* screened parents and siblings of CH patients with TD, in Turkey. They showed that asymptomatic family members of TD revealed an additional 7.4% mild hypoplasia and 3.2% hyperthyrotropinemia without overt hypothyroidism. The results point out the importance of genetic factors in the pathogenesis of CH.[55]

The overall outcome of these studies suggests the possible familial and genetic component in the inheritance of CH. Therefore, genetic studies were designed to determine the genetic basis of CH in our population.

Genetic studies performed in Isfahan CH screening program

Thyroid dyshormonogenesis was the most common etiology of CH in Isfahan, so regarding the elimination of iodine deficiency and the role of TPO gene mutations as the most common causes of thyroid dyshormonogenesis, we designed to determine the prevalence of TPO gene mutations in CH patients with mentioned etiology. However, defects in the TPO gene are reported to be one of the causes of CH due to a total iodide organification defect.[56]

The results of that study demonstrated one missense mutation (G2669A) at exon 15 in 1 patient in

homozygous form and 7 different single nucleotide polymorphisms (SNPs) in exon 1, 7, 8, 11, and 15 of TPO gene, which was less frequent in comparison with other similar studies.[57] We hypothesize that iodine status is the main phenomic modifier of TPO function as reported by Ris-Stalpers and Bikker.[58]

On the other hand, considering that parental consanguinity was more prevalent in dysgenetic CH patients, both in Isfahan and Tehran we design to study the role of *PAX8* gene mutations among these group of CH patients. No mutation or polymorphism was found in studied patients in any of the exons and our results indicate that the *PAX8* mutation rate is very low and can only explain a minority of the cases (unpublished data).

Evidences indicated that thyroid transcription factor 2 (TTF2) gene, known as FOXE1, is involved in the development of thyroid gland and mutations of this gene in a few CH cases with TD, and the presence of TTF2 gene mutations among dysgenetic CH patients was also studied.[55] There was no mutation in TTF2 in our studied CH patients. This was not very surprising since despite the numerous cases of TD patients, only a handful number of cases had mutations in TTF2 gene. Furthermore, we found that the length of the alanine tract of TTF2 was 14 in almost all of our TD patients. This data may point to a role of the TTF2 polyA tract length in modulating genetic susceptibility to TD (unpublished data).

There are ongoing studies, which investigate the role of TSHR gene mutations and DUOX2 in the pathogenesis of CH in Isfahan.

Similar to other studies, these studies support the existence of a familial component of CH involving dominant genetic predisposition factors with a low penetrance. Considering the polygenic/multifactorial basis of CH, our findings suggest the possible involvement of other unknown genes in the pathogenesis of the disease, which may also follow non-Mendelian pattern of inheritance as reported recently.[59,60]

CONCLUSION

In conclusion, although we could not entirely ignore the possible role of environmental and autoimmune factors in the development and function of thyroid gland, our findings strongly suggest the role of genetic factors as dominant etiologic factor in CH. Thus, studying molecular-genetic basis of CH may significantly improve our understanding of the underlying mechanisms of CH pathogenesis, which enhance its diagnosis and proper treatment. In addition, it seems that, researches in this field make possible to introduce genetic examination among CH patients and their relatives to make gene therapy possible for decreasing the prevalence of CH in our community.

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