

Demographic and Clinical Aspects of Congenital Hypothyroidism (Dyshormonogenesis) in Sudan

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Abstract

Introduction: Congenital hypothyroidism is the most common congenital endocrine disorder worldwide. Approximately 80 to 85% of cases are caused by defects in thyroid development (dysgenesis), the remaining 15 to 20% are due to errors of thyroid hormone biosynthesis (dyshormonogenesis). Congenital hypothyroidism is also the most common preventable cause of mental retardation. Its neurological defects can only be reversible if diagnosed and treated early. Its incidence rate is 1 out of 3000/4000 live births worldwide. However, this incidence rate is higher in developing countries such as Sudan (1 of 1400/2200 newborn infants) in which its population is characterized by consanguinity (25-70%).

The present study aimed to assess the demographic and clinical pattern of congenital hypothyroidism (dyshormonogenesis) in Sudan.

Material and Methods: A total of 54 patients referred to Gaffar Ibn Auf Children Hospital presented with clinical features suggesting congenital hypothyroidism (dyshormonogenesis) were enrolled in this study. Demographic and clinical data was obtained by a predesigned questionnaire. Data were analyzed using SPSS 13 software. Descriptive statistics (frequencies and percentages) were obtained for categorical variables.

Results: Most patients enrolled in this study (85.7%) are descendants of consanguineous marriages. There were 11 reported families, comprising 74.3% of cases, with more than one affected member, of those family members, 68.6 % were in fact siblings. Patients from consanguineous marriage had a 96.6% positive family history. The majority of patients (97.1%) developed complications. According to the tribal origin, the vast majority of patients (65.7%) were from Afro-Asiatic tribes, whereas 34.3% were from Nilo-Saharan tribes. There was a large variation in the geographical distribution of patients. Biochemical analysis and ultrasound findings were concordant with the clinical presentation of patients.

Conclusion: 1) Early diagnosis and treatment are crucial to prevent both cognitive and motor detrimental effects of the disease. 2) Consanguineous marriages are a major risk factor in patients with congenital hypothyroidism. 3) There is a wide range of tribal variation of both Afro-Asian (65.7%) and Nilo-Saharan (34.3%) tribes. 4) Poor education and unawareness of the disease were major factors in late diagnosis, treatment and further complications.

Keywords: Congenital Hypothyroidism, Dyshormonogenesis, Sudan.

Congenital hypothyroidism (CH) is the most common congenital

endocrine disorder worldwide. CH is classified into permanent and transient CH. Permanent CH refers to a persistent

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deficiency of thyroid hormone that requires life-long treatment. Transient CH refers to a temporary deficiency of thyroid hormone, discovered at birth, but then recovering to normal thyroid hormone production. Transient hypothyroidism may be caused by maternal or neonatal factors including antithyroid medications, transplacental thyrotropin receptor blocking antibodies and exposure to iodine deficiency or excess. Permanent CH can be further classified into permanent primary and secondary (or central) CH; transient primary CH has also been reported¹.

Permanent congenital hypothyroidism may be due to primary or secondary (central) causes. Primary causes include defects of thyroid gland development, deficiencies in thyroid hormone production, and hypothyroidism resulting from defects of TSH binding or signal transduction. Secondary or central causes include defects at the pituitary, hypothalamus, or hypothalamic portal circulation levels of thyrotropin releasing hormone (TRH) and thyroid stimulating hormone (TSH) production¹.

Primary congenital hypothyroidism is the most common type of hypothyroidism, with dysfunction occurring at the level of the thyroid gland. It is characterized by elevated levels of thyroid-stimulating hormone (TSH) resulting from reduced thyroid function. This disease is caused by disorders of thyroid gland development leading to dysembryogenesis/dysgenesis, (80% – 85%)², in which the gland is either absent (thyroid agenesis) accounting for 35%-45%; unable to descend normally during embryological development with or without ectopy (30%-45%)^{3,4}, or located ectopically and/or severely reduced in size (hypoplasia), which accounts for 5% of cases⁵.

The remaining cases with congenital hypothyroidism (15% - 20%) are due to

congenital errors of thyroid hormone biosynthesis (CDH, congenital dyshormonogenetic hypothyroidism) and are associated with either goitre or a normal thyroid gland^{6,7}.

Congenital hypothyroidism is also the most common preventable cause of mental retardation (cretinism), if early diagnosed and treated⁸. The significant irreversible mental damage can be avoided by the replacement therapy introduced before the age of 3 weeks. Therefore the implementation of screening programs is necessary for early detection and prevention of both cognitive and motor deficits, which are a major feature of this disease^{9,10}.

Neonatal screening programs; launched in the 1970s from North European countries¹¹; have been a major achievement in the detection of CH. It has been proven that early diagnosis and treatment results in normal development in nearly all cases. An additional benefit of neonatal screening has been the elucidation of the incidence of CH as well as the prevalence of its various causes^{12,13}.

The incidence rate of CH is 1 of 3000/4000 live births worldwide¹⁴. However, this incidence rate does not apply to developing countries where consanguineous marriages are common among the population (25-70%). In the Middle East and North Africa region (MENA region) congenital hypothyroidism is even more frequent with an incidence of approximately 1 of 1400/2200 newborn infants^{15,16}.

Consanguineous marriage is a common trend (one-fifth of the world population) in communities residing in the Middle East, West Asia and North Africa, as well as among emigrants from these communities now residing in North America, Europe and Australia¹⁷.

However, in countries like Sudan, little data is available on the frequency of the

disease since there are no established neonatal screening programs. Therefore, we have tried in our study to present a closer look of the presence and effect of congenital hypothyroidism (dys-hormonogenesis) in Sudan. We have included several parameters such as consanguinity, ethnicity, social status, education and family history. Other parameters are symptoms, hormonal investigations, ultrasound findings, treatment and complications of the disease. The present study aimed to assess the demographic and clinical pattern of congenital hypothyroidism (dys-hormonogenesis) in Sudan, to highlight the issue of neonatal screening and to assess the magnitude of the problem.

MATERIALS AND METHODS:

Hospital case records were inspected individually for clinical biochemistry and ultrasound results to confirm the diagnosis and indication for thyroxine replacement including dose and duration. Hospital records were also inspected for weight and height, presence, grade and nodularity of goitre, ultrasound findings, and anti-thyroid antibodies. Thyroid stimulating hormone (TSH) and serum thyroxine concentration (reference ranges: TSH 0.4–4.0 mIU/l, free thyroxine 10–23 pmol/l), results tested at the time of diagnosis, were also recorded.

The following data were recorded directly from the parents/guardians while filling the predesigned study questionnaire: age at onset, age at diagnosis, place of birth, consanguinity, tribe, region (state), education, social status, family history of thyroid disease, family history of deafness, patient's history which includes areas of developmental delay if any.

RESULTS:

Demographic data:

A total of 54 patients with congenital

hypothyroidism were enrolled in this study. Of the 54 patients, 20 (37.1%) were males and 34 (62.9%) were females. The mean frequency of their ages was 10 years and Std. Deviation was 4 years. Age of patients' ranged between 2 and 27 years.

A percentage of 85.7% of our patients came from parents of consanguineous marriages and 14.3% were from non-consanguineous marriage. Of those from non-consanguineous marriages, 40% had both parents of the same tribe and the remaining 60% had parents from different tribes. Families with only one child affected were 25.7%, while others with more than one child posed a high percentage of 74.3%. Of those 74.3%, there were 11 reported families in which 68.6 % of its members were in fact siblings.

According to the tribal origin of patients the vast majority (65.7%) were from Afro-Asiatic tribes, whereas 34.3% were from Nilo-Saharan tribes. Of those Afro-Asiatic tribes, Jaalia was the most common tribe accounting for 31.4% of our patients followed by Shaigia and Maalia, each accounting for 11.4%.

The geographical distribution of the patients showed that the vast majority (22.9% each) were from Alshemalia and Nahr Alneel states, whereas (17.1%) were from Algazeera state followed by (14.3%) from Khartoum state, (11.4%) from Kordofan, Darfur and west Sudan states each accounting for (5.7%).

In terms of education levels the highest percentage (39.4%) was for fathers that received high school education, while mothers that posed the highest percentage (33.3%), had only received primary school education.

Concerning the patients' family history of thyroid disorders, (94.3%) of patients had positive family history.

Regarding social status, most patients (74.3%) came from low social class,

(25.7%) were from middle class while no families had a high social status. Considering patients' place of birth, (62.9%) were born at home, while (37.1%) were born in a health facility.

Clinical data:

Biochemical analysis reports revealed that 60% of patients had both high levels of TSH and low levels of T₄, whereas 14.3% of patients had high levels of TSH with normal levels of T₄. Reports also showed that 17.1% of patients had normal thyroid hormone levels.

Ultrasonography revealed that all patients had normal thyroid glands (normal lobes and isthmus). Patients with goiter represented 88.6%; of those patients (60%) had grade 2, and (22.9%) had grade 1. Patients with nodular goiters represented (28.6%).

Clinical presentations:

Most of the patients (88.6%) presented complaining of neck swelling, (74.3%) had coarse facial features, (42.9%) had protruding tongue, (34.3%) with depressed nasal bridge, (48.6%) have rough dry skin, (71.4%) with fatigue, (37.1%) with prolonged sleeping, (40%) with poor feeding, (37.1%) failed to gain weight, (8.6%) were excessively sweating, (31.4%) with irritability, (14.3%) were excessively crying, (5.7%) had prolonged jaundice, (8.6%) were born with low birth weight, (8.6%) suffered from apnea, (11.4%) were floppy babies, (82.9%) had stunted growth (delayed bone age), and (91.4%) with low IQ.

Complications:

The majority of patients (97.1%) developed complications. The highest percentage accounting for poor school performance (91.4%) followed by gross motor deficient (82.9%), language (speech) (62.9%), fine motor (54.3%), sociality (37.1%), and (11.4%) deafness.

Correlation analysis:

Correlation analysis revealed that there is

negative correlation between parents' education level and age of patients at time of diagnosis and admission, with significance values of 0.001 for fathers' and 0.002 for mothers' education levels.

Correlation analysis also revealed a positive correlation between the age of patients' at time of diagnosis and admission with the appearance of complications.

An inverse relationship between the IQ of patients and his/her age has been proven; IQ score declines as patients' age without being diagnosed and treated.

Patients' weight showed a negative correlation with duration of treatment (p value = 0.00).

Patients' height was also negatively correlated with duration of treatment (p value = 0.00); both indicating non-compliance to treatment.

DISCUSSION:

Most of the patients enrolled in this study (85.7%) are descendants of consanguineous marriages. There were 11 reported families (1st degree relatives), comprising 74.3% of cases, with more than one affected member. Of those family members, 68.6 % were in fact siblings. This data is in accordance with several studies on consanguineous marriage as it is known to have a role in genetic diseases facilitating the expression of rare recessive disease genes (18-20). The offspring of consanguineous relations have an average increased risk of 2-4% of congenital and genetic disorders (20).

Although there were no multi-variant correlation between consanguineous marriage and family history; according to our data, the analysis showed that a high percentage (96.6%) of cases of consanguineous marriage showed positive family history indicating that consanguineous marriage remains the important risk factor in patients with

congenital hypothyroidism. Our data also showed that 40% of patients with non-consanguineous marriage had both parents of the same tribe, indicating that tribal marriages as much as consanguineous marriage in Sudan are deeply rooted traditional and social trends and are highly respect.

The majority of Sudanese tribes belong to two main groups, the Afro-Asian and the Nilo-Saharan. However, the present study revealed that the Afro-Asian were highly involved accounting for (65.7%) followed by the Nilo-Saharan (34.3%).

Patients from different geographical regions are referred to Gaafer Ibn Oaf Specialized Children Hospital, since it is the only hospital in Sudan that has an Endocrinology Unit, and all the cases from all over Sudan come to this hospital to confirm diagnosis and receive proper treatment.

According to the geographical origin of the patients in the present study, it appears that these cases cover almost all the states in Sudan. The majority of cases descended from Alshemalia, Nahr Al neel, Al Gazeera and Khartoum states, all of which are closer to the centre (Gaafer Ibn Oaf Hospital), so they have the benefit of early diagnosis and treatment. Unfortunately, even those patients from the mentioned states arrive at the hospital after developing complications of the disease, as confirmed by a strong correlation between age of patients' at the time of diagnosis and admission and appearance of complications on patients. This is due to several factors. The first comes in accordance to our predesigned questionnaire in that most patients (74.3%) were poor and from a low social status. Therefore, parents were unable to pay for the transportation of their siblings to the centre state to receive medical assistance. In addition to that there is no medical awareness of the disease and its

complications; although medical counselling is carried out; symptoms still pass unnoticed. Another important factor is the education level; strong correlation between level of education of parents and age of patients' at the time of diagnosis and admission was noted; almost 48 – 51% of both parents varied between poor education (primary) and no education (illiterate).

Our data showed that (94.3%) of patients had positive family history of thyroid disorders. This finding is in accordance with several studies that an additional risk of 2-4% of having a child with a genetic/congenital disorder in consanguineous marriage should be added to the basic 2-3% for an average non-consanguineous couple. The risk can further increase if a family history for a genetic disorder exists (20).

With this high percentage of family history including older siblings, patients are still diagnosed and treated at a late stage of the disease shown as; strong correlation between age of patient at time of diagnosis and complications including low IQ.

Correlation analysis has also shown a strong correlation between weight and height, and duration of treatment, leading to the conclusion of non-compliance of the patients.

TPO enzymatic activity is essential for thyroid hormonogenesis. Inactivating *TPO* mutations are the most frequent molecular basis for dyshormonogenetic congenital goitrous hypothyroidism due to iodide organification defects.

Patients with organification defects have a variable degree of primary hypothyroidism and thyroid gland enlargement depending on the severity of the defect. In patients who have not been early diagnosed and treated, a complete defect causes severe hypothyroidism resulting in mental retardation with a large goitre. In our study, we unfortunately found that

only one patient had been early diagnosed and treated, she grew and developed normally, while all the other patients had developed complications of the disease. According to clinical and laboratory findings, patients probably exposed to deleterious effects of thyroid hormone deficiency since the first years of their lives.

Diagnosis of primary hypothyroidism is confirmed by demonstrating decreased levels of serum thyroid hormone (total or free T4) and elevated levels of thyroid-stimulating hormone (TSH). Biochemical analysis from our data showed that 60% of patients had high levels of TSH and low levels of T4 hormones; confirming the diagnosis of CH, whereas 14.3% of patients had high levels of TSH with normal levels of T4; indicating a milder form of CH. A percentage of 17.1% of patients had normal hormone levels; proving that they received treatment prior to admission at Gaafer Ibn Oaf Childrens' Hospital.

Ultrasonography or thyroid scanning is not required to make or confirm the diagnosis of congenital hypothyroidism, but can provide important information about the etiology. It demonstrates the presence of an ectopic thyroid, such as a lingual or sublingual gland, the presence of a bilobed thyroid in the appropriate position or a goiter that suggests an inborn error of thyroid hormone production.

CONCLUSIONS:

1. Early diagnosis and treatment are crucial to prevent both cognitive and motor detrimental effects of the disease, therefore the establishment and implementation of neonatal screening programs is necessary.
2. Consanguineous marriages are a major risk factor in patients with congenital hypothyroidism, as 96.6% of consanguineous marriages have positive family history.

3. There is a wide range of tribal variation; Afro-Asian tribes accounting for (65.7%) and the Nilo-Saharan (34.3%).
4. Poor education and unawareness of the disease were major factors in late diagnosis, treatment and further complications.

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