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Dyshormonogenetic goiter: A clinico-pathologic study of a rare disease with literature review

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Abstract
Introduction: Dyshormonogenetic goiter is a rare inherited disease caused by defects in thyroid hormones synthesis. It mainly affects children and young adults. It is frequently associated with congenital hypothyroidism.
Objective: The aim of our study is to highlight the clinico-pathological characteristics of dyshormonogenetic goiter with a review of literature.
Methods: we reported 4 cases of dyshormonogenetic goiter over a period of 25 years.
Results: There were 2 male and 2 female patients. The mean age was 16 years. All patients were treated with partial or total thyroidectomy and L-thyroxine. Long term follow-up showed relapse in one case and no complications in three cases.
Conclusion: The diagnosis of dyshormonogenetic goiter is suspected in clinical and radiological features and confirmed by histological examination.

Keywords: dyshormonogenetic goiter, thyroid, hyperplasia, hypothyroidism, case report

Introduction

Dyshormonogenetic goiter (DG), also known as thyroid dyshormonogenesis or congenital/familial goiter is a rare inherited disease. Less than 200 cases with detailed morphology have been reported including around 30 cases with cancer [1, 2]. It was firstly described by Osler in 1897 and Pendred in 1896 (1–3). However, genetic defects start to be identified only since 1950 [1]. DG is a multinodular goiter due to defects in thyroid hormones synthesis [1, 3-6]. According to the severity of this defects, patients may be euthyroid or hypothyroid. Clinical and radiological presentations may suggest this disease, but histological exam is the gold standard to confirm the diagnosis and eliminate malignancy.

Objective: The aim of our study is to highlight the clinico-pathological characteristics of dyshormonogenetic goiter with a review of literature.

Methods: We describe 4 cases with dyshormonogenetic goiter. Data were obtained from the files of both Head and Neck Surgery and Pathology Department of FH University Hospital, over a period of 25 years (from 1 January 2005 to 30 September 2021). We follow scare guidelines of 2020 [7].

Results

There were 4 patients. Sex ratio was 1. The mean age was 16 years with extremities ranging from 9 to 22 years. Family history of consanguinity were found in 2 patients. All patients suffered from congenital hypothyroidism since birth or childhood and treated with L- thyroxine. There was no family history and no drugs allergic or psychosocial history. The chief complaint was progressive neck swelling. Physical examination revealed an indolent thyroid enlargement with growth retardation and intellectual disability (Figure 1). Ultrasound and scintigraphy (I^{123}) showed a heterogeneous multinodular goiter suspected to be malignant. Three patients underwent total thyroidectomy and only one had lobo-isthmectomy. The operation was practiced by a professor with 20 years of experience and the head of Head and Neck department of FH University Hospital. After surgery, there were no complications and the patients left the hospital after three days. Macroscopic examination showed a goiter with numerous colloid nodules and interfollicular fibrosis (Figure 2). On microscopic analysis, nodules were hypercellular with macro and microfollicular patterns (Figure 3). Internodular background had focal cellular pleomorphism and nuclear atypia surrounded by fibrosis (Figure 3). There was no normal thyroid tissue

(Figure 3). The diagnosis of dyshormonogenetic goiter was made. Long-term follow-up was without any complication or relapse.

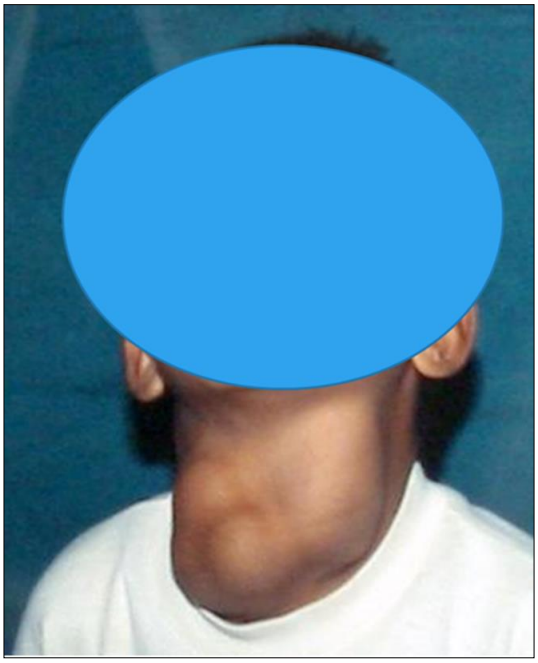

Fig 1: Physical examination showed thyroid enlargement with multiple nodules

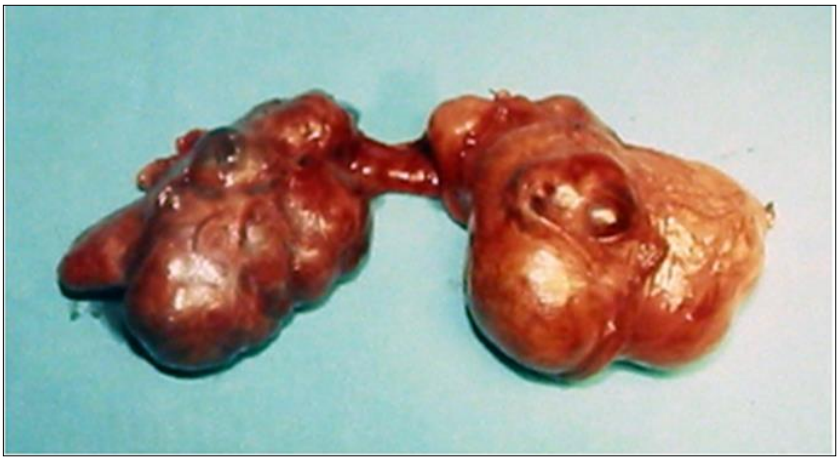

Fig 2: Macroscopic examination showed thyroid enlargement with multiple nodules

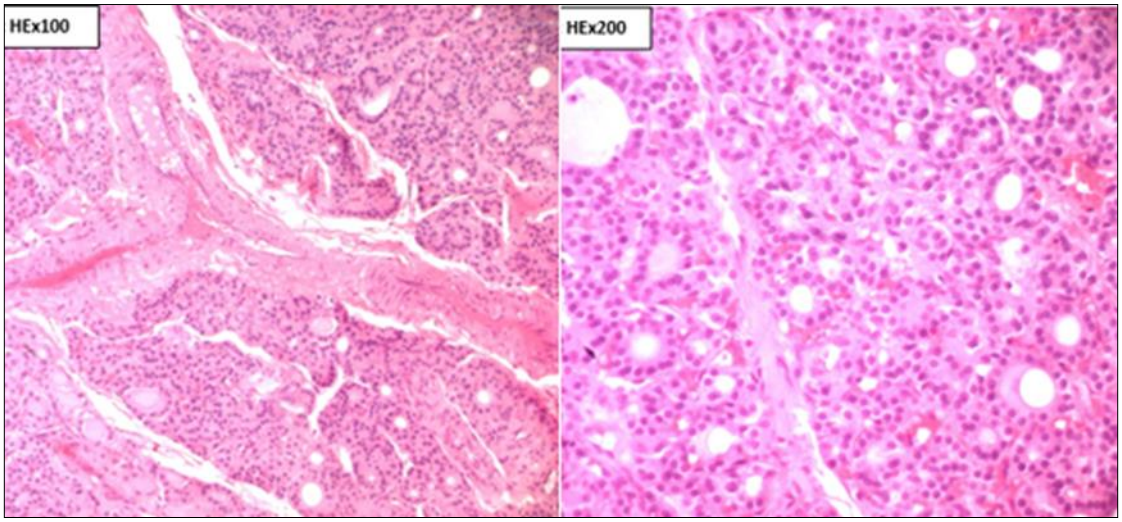

Fig 3: Microscopic analysis shows hypercellular nodules with macro, microfollicular patterns and internodular background with focal cellular pleomorphism and nuclear atypia surrounded by fibrosis

Conclusion

Dyshormonogenetic goiter is the second cause of congenital hypothyroidism, after thyroid dysgenesis [3, 4, 6, 8, 9]. This diseases accounts for 10 to 15% of congenital hypothyroidism [3, 4, 6, 8, 9]. It mostly affects woman with a sex-ratio of 0,5. The incidence of this disorder is about 1 per 30.000-50.000 live birth [3, 4, 6, 8, 9]. The mean age is 16 years with extremes ranging between newborn and 52 years [9-12]. 80% of patients are aged less than 25 years (9,11,12). Consanguinity are detected in most patients [3, 6, 8, 11]. There are no ethnic or racial predilections [11].

The pathogenesis of DG is still unclear until now. Several studies described mutation in genes that encode for enzymes implicated in thyroid hormones biosynthesis [3, 5, 6, 8]. There are 7 genes: NIS/SLC5A5, PDS/SLC26A4, TG, TPO, DUOX2, DUOXA2 and YID/DEHAL1 [13]. TG and TPO are the most implicated ones (6,8,14). TG participate in thyroglobulin biosynthesis, DUOX2, DUOXA2 in H2O2 generation and TPO in iodide organification and in coupling of mono- and diiodotyrosine. NIS/SLC5A5 and PDS/SLC26A4 are involved in iodide transport [3, 5, 6, 8]. IYD/DEHAL1 interfere in proteolytic breakdown of thyroglobulin and in iodide recycling [3, 5, 6, 8]. All these genetic disorders lead to a loss of T3 and T4 synthesis, overproduction of TSH and thyroid gland hyperplasia [3, 4, 6]. Mode of DG inheritance is mainly autosomal recessive except for DUOX2 which can be autosomal dominant [3, 4, 6, 8-10, 12].

DG is rarely associated with malformations omitting Pendred syndrome [15]. The latter is an autosomal recessive disease defined by congenital goiter, deafness and mutism [16]. The hallmark of this syndrome is mutations in PDS/SLC26A4 gene encoding for pendrin [16].

The clinical presentation of DG include congenital hypothyroidism and thyroid enlargement with growth and intellectual deficiencies depending on the importance of metabolic error [3, 6, 8]. The earlier enzyme defects occur in the pathway of hormone synthesis, the more severe symptoms are [3, 9].

Ultrasound is usually practiced to confirm the diagnosis of multinodular goiter and to rule out malignancy. It reveals multiple hypoechoic nodules with thyroid hypertrophy [17]. Scintigraphy using Iodine 123 (I^{123}) or Technetium 99m (Tc^{99m}) is recommended to classify DG. Indeed, scintigraphy, for patients with iodide transport defect (NIS/SLC5A5 and PDS/SLC26A4), detects no or low radioiodine uptake in thyroid gland ("white scintigraphy") [3, 12, 18]. However, for patients with iodine organification defect (TPO, DUOX2, DUOXA2), radioactive iodine uptake is normal at 4 hour and slightly increasing at 24 hour. Then, potassium perchlorate discharge test is performed. This test shows a washout of the radiotracer in contrast of normal thyroid tissue [3, 12, 18]. Patients with TG and DEHAL1 mutations present normal radioiodine uptake and normal potassium perchlorate test [3, 12, 18].

Treatment of DG required T4 replacement therapy with L-thyroxine since congenital hypothyroidism is revealed [3, 4, 6]. Total or partial thyroidectomy is recommended when malignancy is suspected or for cosmetics reasons or when goiter is too large leading to complications like dysphagia and dyspnea [3, 4, 6, 19].

Macroscopically, DG displays an enlarged thyroid with multiple pale nodules and large internodular fibrosis [3, 4, 6]. On histological examination, there is no normal thyroid tissue. Nodules are hypercellular with a solid or micro or macrofollicular patterns, sometimes papillary and insular hyperplasia [3, 4, 6, 19]. Papillae are usually simples. Colloid is minimal to absent. The follicular cells exhibit marked nuclear atypia with enlarged, irregularly shaped, hyperchromatic and bizarre nuclei. These nuclear atypia are more common in internodular tissue than in nodules [3, 4, 6]. The nodules are entrapped with extensive bridging fibrosis which can simulate malignancy [3, 4, 6]. Immunohistostaining is not needed for the diagnosis [3, 4, 6].

DG has usually an excellent prognosis when it is diagnosed and treated early [3, 6]. Mental retardation and growth disability are the most common complications [3, 4]. Cancers arise rarely in DG. The most frequent tumors are follicular and papillary carcinoma [20].

Genetic screening is nowadays carried out for an early diagnosis to avoid complications.

The main differential diagnoses are endemic multinodular goiter, radiation thyroiditis, iatrogenic goiter, Graves disease and papillary carcinoma [3, 6].

Endemic multinodular goiter (EMG) is the chief differential diagnosis. Clinically, DG is usually associated with congenital hypothyroidism and EMG with euthyroidism. Macroscopically, both DG and EMG have similar gross appearance. Histologic analysis is essential for the diagnosis. EMG is characterized by hyperplasia limited to nodules with normal thyroid tissue between nodules [3, 6].

Radiation thyroiditis and iatrogenic goiter have identical macroscopic and histologic features. Diffuse nuclear atypia may suspect both diseases. The history of thyroid radiation or thionamides treatments of patient or mother eliminates the diagnosis of DG [3, 6].

Graves disease is characterized clinically by euthyroidism and histologically by diffuse hyperplasia without any nodule or nuclear atypia [3, 6]. However, DG is associated with congenital hypothyroidism and nodular hyperplasia surrounded by fibrosis.

The prominent papillary patterns may mimic papillary carcinoma but in DG, the papillae are simples and cells has no nuclear criteria of papillary carcinoma as nuclear enlargement, chromatin clearing, irregular nuclear contour, nuclear grooves and nuclear pseudoinclusions [3, 6, 9, 10].

In conclusion, dyshormonogenetic goiter is a rare benign and congenital disease. Diagnosis may be suspected in a children or young adult with multinodular goiter and congenital hypothyroidism. Histopathological examination is the gold standard. Cellular pleomorphism and nuclear atypia can mimic thyroid cancer. This condition is generally treated with surgical approach and T4 replacement therapy with L-thyroxine.

List of abbreviation
DG: dyshormonogenetic goiter
I^{123}: Iodine 123
Tc^{99m}: Technetium 99m
EMG: endemic multinodular goiter

Declarations
Ethical approval and consent to participate
This study is exempt from ethical approval at our institution.

Consent of Patient
Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Availability of data and material
The authors declare that there are that all data and materials are available.

Competing interests
The authors declare no competing interest associated with this manuscript

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Conflict of interest
The authors have no conflict of interest to disclose.

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References
1. Knobel M, Medeiros-Neto G. An outline of inherited disorders of the thyroid hormone generating system. Thyroid,2003:13(8):771-801.
2. Matos PS, Bisi H, Medeiros-Neto G. Dyshormonogenetic goiter: A morphological and immunohistochemical study. Endocr Pathol,1994:5(1):49–58.
3. Momin Y, H. Ansari SA. Dyshormonongenetic goiter: A rare and important entity. Arch Med Health Sci,2020:8(1):88.
4. Thompson L. Dyshormonogenetic goiter of the thyroid gland. Ear Nose Throat J,2005:84(4):200.
5. Ramesh BG, Bhargav PR, Rajesh BG, Devi NV, Vijayaraghavan R, Varma BA. Genotype-phenotype correlations of dyshormonogenetic goiter in children and adolescents from South India. Indian J Endocrinol Metab,2016:20(6):816–24.
6. Braham E, Ben Rejeb H, Marghli A, Kilani T, El Mezni F. A rare and particular form of goiter to recognize. Ann Transl Med,2013:1(2):21.
7. Agha RA, Franchi T, Sohrabi C, Mathew G, Kerwan A, SCARE Group. The SCARE 2020 Guideline: Updating Consensus Surgical CAse REport (SCARE) Guidelines. Int J Surg,2020:84:226–30.
8. Cangul H, Aycan Z, Olivera-Nappa A, Saglam H, Schoenmakers NA, Boelaert K, *et al*. Thyroid dyshormonogenesis is mainly caused by TPO mutations in consanguineous community. Clin Endocrinol (Oxf),2013:79(2):275–81.
9. Fadda G, Baloch ZW, LiVolsi VA. Dyshormonogenetic Goiter Pathology: A Review. Int J Surg Pathol,1999:7(3):125–31.
10. Ghossein RA, Rosai J, Heffess C. Dyshormonogenetic Goiter: A Clinicopathologic Study of 56 Cases. Endocr Pathol,1997:8(4):283–92.
11. Stoppa-Vaucher S, Van Vliet G, Deladoëy J. Variation by ethnicity in the prevalence of congenital hypothyroidism due to thyroid dysgenesis. Thyroid,2011:21(1):13–8.
12. Szinnai G. Clinical genetics of congenital hypothyroidism. Endocr Dev,2014:26:60–78.
13. Kwak MJ. Clinical genetics of defects in thyroid hormone synthesis. Ann Pediatr Endocrinol Metab,2018:23(4):169–75.
14. Lacka K, Maciejewski A. Rare thyroid non-neoplastic diseases. Thyroid Res,2015:8(1):5.
15. Léger J, Olivieri A, Donaldson M, Torresani T, Krude H, van Vliet G, *et al*. European Society for Paediatric Endocrinology Consensus Guidelines on Screening, Diagnosis, and Management of Congenital Hypothyroidism. The Journal of Clinical Endocrinology & Metabolism,2014:99(2):363–84.
16. Wémeau J-L, Kopp P. Pendred syndrome. Best Practice & Research Clinical Endocrinology & Metabolism,2017:31(2):213–24.

17. Hong HS, Lee EH, Jeong SH, Park J, Lee H. Ultrasonography of various thyroid diseases in children and adolescents: a pictorial essay. Korean J Radiol,2015:16(2):419–29.
18. Williams JL, Paul DL, Bisset G. Thyroid disease in children: part 1: State-of-the-art imaging in pediatric hypothyroidism. Pediatr Radiol,2013:43(10):1244–53.
19. Deshpande AH, Bobhate SK. Cytological features of dyshormonogenetic goiter: Case report and review of the literature. Diagn Cytopathol,2005:33(4):252–4.
20. Kallel R, Mnif Hachicha L, Mnif M, Hammami B, Ayadi L, Bahri I, *et al*. [Papillary carcinoma arising from dyshormonogenetic goiter]. Ann Endocrinol (Paris),2009:70(6):485-8.