PENDRED'S SYNDROME; A CASE REPORT AND REVIEW OF LITERATURES

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ABSTRACT

Thyroid dyshormonogenesis is a rare condition, due to genetic defects in the synthesis of thyroid hormones where patients develop hypothyroidism with goiter. One particular familial form , associated with sensorineural deafness is called Pendred's Syndrome (PS).

We report probably a unique case of a young man with PS who developed a large, bulky goiter without a family history of goiter or deafness. The clinical findings were used to illustrate the normal physiology of thyroid hormone synthesis, the mechanisms of iodide transport in the thyrocyte, the pathophysiology of dyhormonogenesis and genetics of Pendred's syndrome.

INTRODUCTION

The thyroid gland synthesizes and releases thyroxin (T4) and tri-iodothyronine (T3) in a ratio of 4:1. This is controlled by thyroid stimulating hormone (TSH), synthesized by the anterior lobe of pituitary and released in response to thyrotrophin-releasing hormone (TRH) which is secreted from the neurons of the paraventicular nucleus into the hypophyseal portal circulation. TRH and TSH synthesis and release are regulated by negative feedback of circulating thyroid hormones.[1] The iodine pathway comprises several steps in thyroid cells that involve an iodide transport mechanism via the sodium/iodide symporter (NIS), iodide organification into the thyroglobulin molecule at the apical pole that is mediated by the Thyroid Peroxidase and thyroid hormone synthesis and secretion.[2] Pendred's Syndrome (PS) is an autosomal recessive disorder characterized by congenital sensorineural hearing loss and progressive enlarging goiter. First, it was recognized by Vaughan Pendred, British physician, in two members of a large family in 1896. [3] The most prominent and obligatory clinical sign in patients with Pendred's syndrome is profound sensorineural hearing impairment. In most individuals, deafness is prelingual, but it may be progressive and become apparent only later in childhood.[4] Patients with Pendred's Syndrome often have a malformation of the inner ear referred to as Mondini defect in which the cochlear turns are replaced by a rudimentary cochlea or a single cavity, the Mondini defect is, however, not specific for Pendred's syndrome nor present in all patients.[5]. (Figure-1).[6] The thyroid enlargement in Pendred's syndrome typically develops during childhood, being variable both between families and within the same family. Iodine deficiency has been recognized as a modifying factor, thus the prevalence of goiters may be lower in patients with Pendred's syndrome living in iodine-replete regions. http://www.medicinenet.com/pendred_syndrome

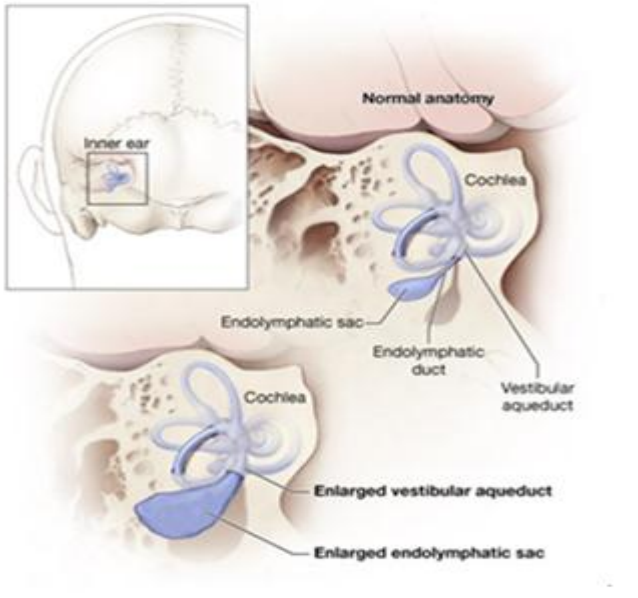

Figure-1- a large vestibular aqueduct with enlargement of the endolymphatic sac and duct.

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The molecular basis of Pendred's syndrome has been unraveled through the cloning of the PS (Pendred syndrome) gene located on chromosome 7q31. The PS gene encodes a highly hydrophobic membrane protein referred to as pendrin, which is predominantly expressed in the thyroid, the inner ear, and the kidney. Functionally, pendrin is a chloride/iodide transporter, in thyroid follicular cells pendrin is inserted into the apical membrane suggesting a possible role in iodide transport into the follicle, but its exact role in the physiology of the thyroid and the inner ear remains to be defined.[8] Mutations in the gene encoding the anion transporter, SLC26A4, also termed "Pendrin" were found in affected patients.[9] No specific treatment exists for Pendred's syndrome. Speech and language support, and cochlear implants, may improve language skills. If thyroid hormone levels are decreased, thyroxine may be required. [10]

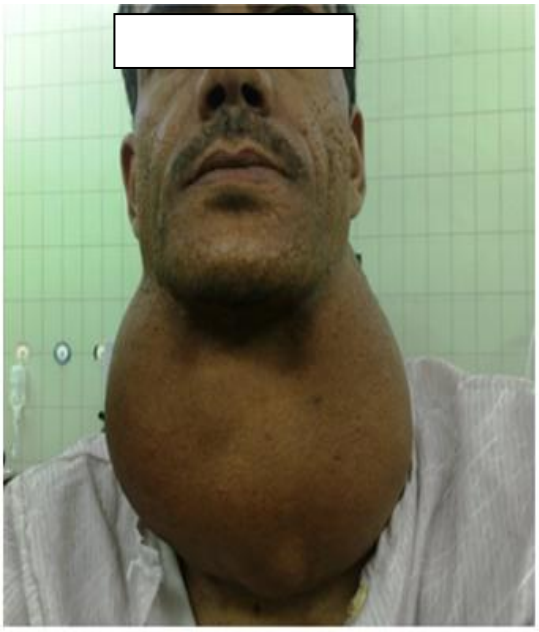

Figure-2-Pendred's Syndrome before thyroidectomy

The Case report

36 years old unmarried male (Figures 2 and 3) presented to our hospital with history of deafness and mutism since early childhood, followed by gradually increasing goiter in adulthood causing progressive dyspnea and difficulty in sleep. Physical examination revealed big multinodular goiter occupying the anterior and lateral compartments of the neck with poscillated thyroid surface and prominent isthmus. The goiter was not tender, nor bruit was found on auscultation. Thyroid function test showed euthyroid state. Other blood investigations were normal. Ultrasound examination confirmed multinodularty. Indirect laryngoscopy confirmed mobile both vocal cords. A written informed consent was obtained from the patient and his family for publication of this case with its accompanying images. Operation was performed under general anesthesia with endotracheal tube. One pint of compatible blood was transfused during operation. Total thyroidectomy was performed (Figure-4) and the patient had smooth postoperative period. The patient was postoperatively kept on perminant replacement therapy with Thyroxin (100 micg tablets) one tablet/ day.

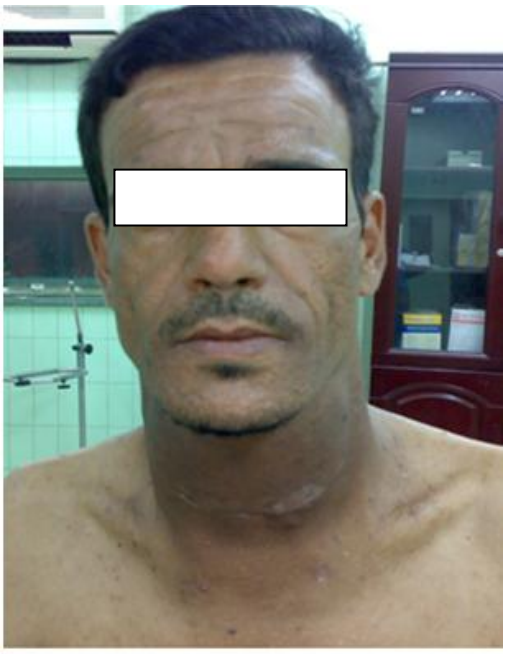

Figure-3-Pendred'Syndrome after thyroidectomy

Pathology

Gross Pathology (Figure-4)

Two thyroid tissues ; each was about 14x10x7 cm, grey brown in color, nodular with colloid, heamorrhage and calcification.

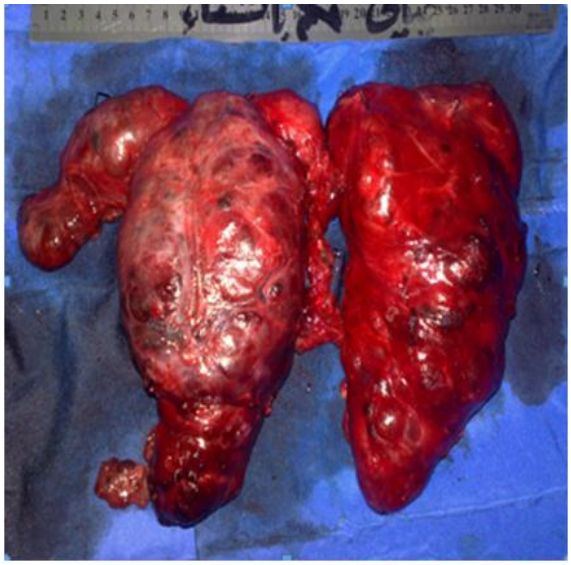

Figure-4-The thyroid specimen after thyroidectomy

Microscopic Pathology (Figure -5)

Benign thyroid tissue; thyroid follicles were filled with colloid, extensive fibrosis, calcifications and congestion.

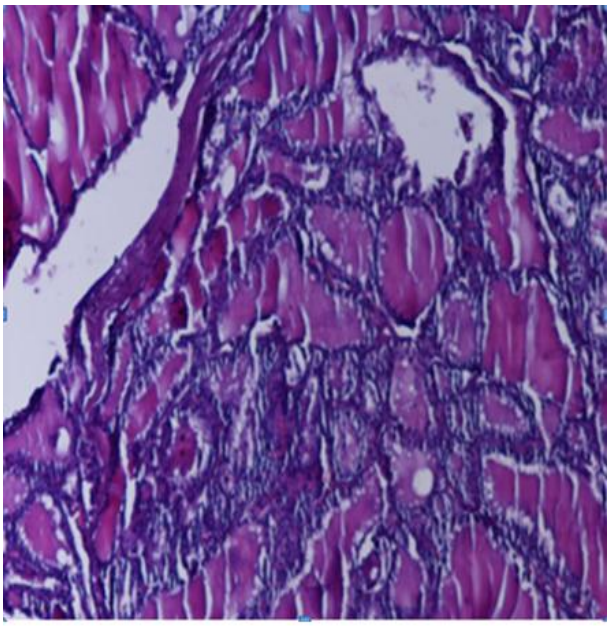

Figure-5- thyroid follicles were filled with colloid with extensive fibrosis, calcifications and congestion.

DISCUSSION

Pendred's syndrome, also known the goiter-deafness syndrome is a genetic disease characterized by association between congenital sensorineural deafness and goiter. It was clinically recognized and concisely described in two sisters in 1896 by the English general practitioner Vaughan Pendred (1869-1946). But the disorder was only more widely recognized following the reports of further sibships by Brain in 1927. It is inherited as an autosomal recessive trait. It has recently been mapped to q31 coincident with the non-syndromic deafness locus DFNB4.Study of a larger population based sample, concluded that Pendred syndrome is characteristically segregated as an autosomal recessive disorder.[11] Although this disease was described more than a hundred years ago, it remains unknown to most physicians in clinical practice, and its diagnosis is often missed. A possible reason for this situation is the highly variable course of both the hearing impairment and the thyroid dysfunction. It seems that many patients with this disease may benefit from early diagnosis and treatment. Interestingly, two major clinical manifestations of Pendred syndrome, congenital hypothyroidism (frequency 1:4000) and congenital hearing impairment (frequency approximately 1 to 2:2 000) can now be diagnosed in the neonatal period.[12] Typically, affected subjects demonstrate avid thyroidal iodide uptake but impaired iodide organification, as determined by an exaggerated release of uncoupled radioiodine tracer from the thyroid following perchlorate administration (a positive perchlorate discharge test). [13] Indeed, goiter does not appear to be an essential prerequisite for the diagnosis of Pendred's syndrome, because it is absent in 50% of reported cases. If present, it varies from a slight enlargement to a large multinodular goiter, probably in relation to different degrees of iodine deficiency. Most patients are euthyroid, independently of the presence of goiter, but some show hypothyroidism. However, the incidence of the syndrome was evaluated on the basis of clinical studies that were frequently incomplete and underscored the fact that the phenotype of patients with Pendred's syndrome differs

greatly among families and even within the same family, leading to pitfalls in the diagnosis.[14] In this report we present a case of Pendred's syndrome with no family history of deafness or goiter who presented with deafness and mutism since early childhood, followed by gradually increasing goiter in adulthood. He was euthyroid at time of presentation. The diagnosis of Pendred syndrome was made clinically. The tests for mutation were not available. In the study of William, et al.[13] goiter was present in 43 (83%) of the cohort, generally developed after the age of 10 years, 56% remained euthyroid (age range 9-37 years), and 19 patients (44%) had objective evidence of hypothyroidism, all of them had goiter. The thyroid phenotype was also highly variable within the family, with thyroid sizes ranging from normal to large goiters requiring thyroidectomy. In the study of Napiontek U et al, led to the conclusion that other environmental and/or genetic factors have an impact on the PS phenotype.[15] In this case, total thyroidectomy was performed due to bulky goiter causing tracheal compression. Management of a patient with Pendred syndrome requires careful follow-up and regular imaging of the thyroid. Although the therapeutic approach to dyshormonogenetic goitres is still controversial. Banghova K, et al suggested total thyroidectomy as the most advantageous method to prevent the development of malignancies that may arise more frequently from dyshormonogenetic goitres than from goitres of other aetiologies.[16,17]

CONCLUSION AND RECOMMENDATION

Securing the diagnosis of Pendred syndrome is important, not just in terms of management of the thyroid dysfunction, but also for genetic counseling purposes. This is especially true in case where the identification of the syndrome would clearly signal the 25% recurrence risk applicable to the couple. To the best of our knowledge, it is the first reported case with such large goiter in our territory. It is advisable to work within cooperative groups for the treatment of rare cases and reporting such cases will probably be the way to move forwards in the management of these cases.

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