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Clinical and Biological Characteristics of Congenital Hypothyroidism: A Family Case Study

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Authors' contributions

This work was carried out in collaboration among all authors. Authors NM and AG designed the study, performed the statistical analysis, wrote the protocol, wrote the first draft of the manuscript, and managed the analyses of the study. Authors NM and AG managed the literature searches. Author AT performed the genetic study. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Hypothyroidism is the condition of thyroid hormone deficiency. It can be primary or acquired. Primary hypothyroidism can be congenital or late onset. The symptoms of congenital hypothyroidism may go unnoticed in newborns if undiagnosed. Untreated, hypothyroidism can lead to poor mental and intellectual development in children. Hypothyroidism's clinical manifestations are often subtle or not present at birth. Common symptoms include decreased activity and increased sleep, feeding difficulty, and constipation. On examination, common signs include myxoedematous facies, large fontanels, macroglossia, a distended abdomen with umbilical hernia, and hypotonia. Levothyroxine is the treatment of choice. In general, the prognosis is excellent when this condition is detected by screening and started on treatment early.

Keywords: Congenital hypothyroidism; newborn; early treatment.

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1. INTRODUCTION

Congenital hypothyroidism (CH) is the most common preventable cause of mental and motor retardation in infants, with an incidence of 1:2000 to 1:4000.1 With the development of molecular biotechnology, novel perspectives on the pathogenesis of CH have been reported. To date, numerous studies have reported genetic causes in CH patients, and several lines of evidence support a relevant genetic origin for CH [1,2].

According to the causes of the underlying mutated genes, the genetic classification divides CH into two main categories, thyroid dysgenesis and thyroid dyshormonogenesis. These disorders lead to primary hypothyroidism. Most commonly, dyshormonogenesis is due to defects of thyroid peroxidase activity [3] Severe defects in this enzyme lead to total iodide organification defects (TIOD). This diagnosis is made by showing high radioactive iodine (RAI) uptake of the thyroid gland followed by more than 90% release after sodium perchlorate administration [4]. Pendred's syndrome is a well-known form of syndromic hypothyroidism and is characterized by a triad of hypothyroidism, goiter and deafness. This syndrome is caused by a genetic defect in the transmembrane protein pendrin (encoded on 7q31).

Defects in pendrin lead to impaired iodide organification and these patients have a positive perchlorate discharge test [5]. More recently, mutations in the enzyme dual oxidase 2 (known as DUOX2 or THOX2) have been found. They lead to dyshormonogenesis from deficient hydrogen peroxide [6]. Mutations in the dual oxidase maturation factor (DUOXA2) gene also lead to deficient iodide organification [7]. Other rare causes of dyshormonogenesis include defects in sodium/iodide transport, resulting from a mutation in the gene encoding the sodium-iodide symporter [8], and defective thyroglobulin action, resulting from a mutation in the gene encoding thyroglobulin [9]. A defect in the enzyme iodotyrosine deiodinase which aids in the peripheral conversion of T4 to T3 has been shown in hypothyroid individuals. This can be due to homozygous mutations in the genes DEHAL1 or SECISBP2 [10,11].

Congenital secondary or central hypothyroidism generally results from defects of TSH production; most commonly, it is part of a disorder causing congenital hypopituitarism. Congenital hypopituitarism often is associated with midline defects such as septo-optic dysplasia or cleft lip and/or palate and can be part of a larger genetic syndrome. Mutations in genes regulating pituitary gland development, which include HESX1, LHX3, LHX4, PIT1 and PROP1 have been reported to be a cause of familial hypopituitarism. Besides TSH deficiency, other pituitary hormones are often deficient, including growth hormone, adrenocorticotrophic hormone and antidiuretic hormone. Rarely, specific gene defects lead to central hypothyroidism. These include isolated TSH deficiency (autosomal recessive, caused by mutations in the TSH β subunit gene), and thyrotropin releasing hormone (TRH) resistance, resulting from mutations in the TRH receptor gene [22,24].

Congenital TSH deficiency can rarely be an isolated problem (caused by mutations in the TSH subunit gene), but it is most often associated with other pituitary hormone deficiencies, as part of a congenital hypopituitarism. Peripheral hypothyroidism is a separate category resulting from abnormalities in the transport, metabolism or action of thyroid hormones [25,26].

Congenital hypothyroidism is classified as permanent and transient CH. Permanent CH refers to a persistent thyroid hormone deficiency that requires lifelong treatment. Transient HC refers to a temporary deficiency of thyroid hormone, discovered at birth, but which then recovers to normal thyroid hormone production. Cure for euthyroidism usually occurs in the first few months or years of life. Permanent CH can be classified as primary and secondary (or central) permanent CH; Transient primary CH has also been reported. In addition, some forms of CH are associated with defects in other organ systems; these are classified as syndromic hypothyroidism [23,24].

The underlying etiology of HC will usually determine whether the hypothyroidism is permanent or transient, primary, secondary or peripheral, and whether there is involvement of other organ systems. It should be borne in mind that an underlying etiology may not be determined for many cases of CH. In addition, while the exact cause of some cases of thyroid dysgenesis is known, for example a mutation in the TTF-2 gene, mutations in genes encoding such transcription factors important in the development of the thyroid gland have not been were found only in 2% of cases. Thus, the exact

cause of the vast majority of cases of thyroid dysgenesis remains unknown. However, this has not been a major problem, as the management of HC is based on restoring thyroid function to normal, without necessarily knowing the exact underlying cause.

In the neonatal period, the clinical manifestations are often not very suggestive, which makes the diagnosis difficult [1]. The clinical features of congenital hypothyroidism are often subtle and many newborn infants remain undiagnosed at birth [2]. This is due in part to passage of maternal thyroid hormone across the placenta, as the measured amount of the hormone in umbilical cord serum to be 25-50 percent of normal [3]. This hormone transfer provides a protective effect, especially to the fetal brain [4].

In the most common form of congenital hypothyroidism, some moderately functioning thyroid tissue can still be found [5]. Because obvious clinical symptoms develop slowly [6], and it is important to start treatment early, several countries (e.g., France, and US) implemented programs of widespread newborn screening for this condition [7]. Unfortunately, newborn screening for hypothyroidism is not done in many third world countries, and only an estimated 1/3 of the worldwide birth population is screened. It is therefore important that clinicians be able to recognize and treat the disorder.

We report the cases of three girls from the same family treated for congenital hypothyroidism complicated by multi-heteronodular goiter in the first daughter and a pituitary tumor in the second. In the third daughter, the genetic study of the panel of genes by NGS sequencing demonstrated the presence of a variant in the homozygous state of the gene (NIS) which codes for the transport of iodine located at the level of the basement membrane of the thyroid follicular cell. We stress the need for early and well-conducted diagnosis and treatment to avoid possible complications.

2. REPORT

Case 1: Infant of two and a half years, admitted to the service at the age of 5 weeks, 4th of a sibling of 5, born via vaginal delivery to consanguineous parents. The pregnancy not followed. The infant, whose birth weight was 4000 g, had good adaptation to extrauterine life, exclusive breastfeeding, and meconium emitted during the first 24 hours of life.

The clinical signs on admission were hypotonia, gross facies, infiltration of the eyelids, macroglossia with swallowing disorder, constipation, large and soft stomach, umbilical hernia. When admitted to our unit, the patient's weight was 5100g (+ 2DS).

Interrogation of the parents revealed that the patient has two sisters: SC who was followed for hypothyroidism and operated on for multi-heteronodular goiter, and MC who was followed for hypothyroidism, operated on for pituitary tumor and then died.

Based on the patient's clinical picture and family history, hypothyroidism was suspected and then confirmed biologically: TSHus = 466.95 µIU/ml; FT4 = 0.42mg/dl; FT3 = 1.72pg/ml. The dosage of anti-TSH receptor antibodies was less than 0.3 IU/l. Thyroid ultrasound was normal, pituitary MRI was normal. An abnormality in the hormonosynthesis of thyroid hormones was suggested and confirmed by the genetic study. The analysis of the gene panel by next-generation sequencing demonstrated the presence of a variant with the homozygous state of the gene that codes for the transport of iodine located at the basement membrane of the follicular cell.

The patient was quickly put on thyroid hormone replacement therapy (levothyrox) and had good clinical and biological progress after a follow-up of two and a half years. During continuous monitoring, the patient had good height-weight and psychomotor development.

Case 2: SC, sister of YC, is the second child in the family, aged 18, born at term vaginally, with a birth weight of 4000 g. The parents had observed that their daughter was too calm and unresponsive. It was not until the age of 8 months that the diagnosis of hypothyroidism was made, at which time the patient was put on thyroid hormone replacement therapy. Unfortunately the parents had stopped the regular follow-up with the physician and gave the treatment to their daughter irregularly. When SC presented with a cervical nodule (at the age of 8 years), a cervical ultrasound was performed and it showed a multiuteronodular goiter classified Trads 3 on the right and Trads 4 on the left. A fine needle aspiration of a thyroid nodule did not yield a diagnostic according to the Bethesda 2010 classification. The patient therefore underwent a total thyroidectomy. The anatomopathological study was in favor of a

Infant with congenital hypothyroidism.

A. 1 month old infantwith CH; picture demonstrates hypotonic posture, myxedematous facies, macroglossia, abdominal distension and umbilical hernia
B. Same infant, after 29 months of treatment and regular follow-up.

dyshormonogenetic goiter with the presence of a neoplasm in the left lobe. Non-invasive follicular thyroid with papillary-type nucleus (NIFTP according to WHO 2017) measuring 6 mm in diameter and an infra-millimeter papillary micro carcinoma in the right lobe with low risk of recurrence. Complications were marked by the onset of hypoparatyhroidism, and the patient was added to Levothyrox, under calcidia plus unalphales. Regular check-ups showed that the patient was delayed in weight and had school difficulties. The genetic study of SC is ongoing.

Case 3: MC: fourth sister of YC, whose clinical signs were observed by the parents at 4 months of life in the form of hypotonia, macroglossia, and an abnormal level of calm. The diagnosis of hypothyroidism was confirmed by assay of TSH and thyroid hormones. Cervical ultrasound showed that the thyroid gland is in place. The patient was put on thyroid hormone replacement therapy. The evolution was marked by the onset of headache. After 5 years of evolution of hypothyroidism, a cerebral MRI revealed a pituitary tumor for which she was operated, and the patient died 3 months after the surgery.

3. DISCUSSION

The incidence of congenital hypothyroidism varies from country to country, the low incidence of this pathology in developing countries [12,13] may change with systematic screening. Early detection and management of congenital hypothyroidism may also reduce complications, especially mental and intellectual retardation [14-16]. Early treatment should be started during the first two weeks of life to have good results [17].

Early TDH diagnosis and treatment are essential for normal brain development and physical growth Over the past two decades, the increased incidence of TDH associated with the high heterogeneity of its biological spectrum has been investigated. Relative to the technical limitations of direct sequencing for diagnosis, recent studies have demonstrated the efficiency of next-generation sequencing technology for CH screening [18].

Clinical signs are often inconspicuous or absent at birth, possibly due to transplacental passage of maternal thyroid hormone and residual thyroid production in many children. Specific symptoms

often do not appear for several months. They include hypoactivity with heavy sleep, difficulty sucking, constipation, myxedematous facies, large fontanelles (especially posterior), macroglossia, abdominal distension with umbilical hernia and hypotonia. Slow growth and developmental delay are usually noticeable around 4 to 6 months of age [19,13]. If left untreated, the disease leads to intellectual deficit and short stature.

Faced with these signs, hypothyroidism must be evoked and confirmed by the TSH assay which would show high levels (> 100 mIU / L in our case). Barry et al. [20] noted in their series that 65.7% of hypothyroid newborns had a TSH greater than or equal to 100 mIU /l. The TSH test is the first diagnostic test to order if you suspect congenital hypothyroidism. The low level of other thyroid hormones (T4 and T3) confirms this diagnosis. The very high TSH value would be in favor of a thyroid origin of congenital hypothyroidism. This origin may be athyreosis, glandular ectopia [21] or thyroid dysgenesis [20]. The ultrasound performed on our patients eliminated these hypotheses by showing a gland in place. The other tests, in particular the assay of anti-thyroperoxidase antibodies and anti-thyroglobulin antibodies which had normal values, confirm the primary nature of hypothyroidism. However, an etiological assessment made by the laboratory of analysis and molecular biology of the Faculty of Medicine of Rabat revealed that the mutation mentioned earlier of the NIS gene (sodium iodide symporter), was in progress in patient SC. A familial form of HC will guide genetic counseling. The etiological diagnosis is not necessary to start hormone therapy. This treatment is based on levothyroxine that we administered to patient YC at day 40 of life. Unfortunately the treatment was administered too late to patient SC because of the parents had brought their daughter to consult in time. This led to complications of mental retardation and stature of SC and a progression to multiheteronodular goiter.

Levothyroxine is the treatment of choice; the recommended starting dose is 10 to 15 mcg / kg / day. The immediate goals of treatment are to rapidly raise the serum T4 above 130 nmol / L (10 ug / dL) and normalize serum TSH levels. Frequent laboratory monitoring in infancy is essential to ensure optimal neurocognitive outcome. Serum TSH and free T4 should be measured every 1- 2 months in the first 6 months of life and every 3-4 months thereafter.

4. CONCLUSION

Hypothyroidism is the most common endocrine disease in the neonatal period. These family cases show the need for early diagnosis and treatment in the face of clinical signs. Better still, systematic screening during the neonatal period would prevent complications. The discovery of a familial form of HC will guide genetic counseling.

CONSENT

Consent was taken from the parents of the patient.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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