OPEN ACCESS
Saudi Journal of Medicine
Abbreviated Key Title: Saudi J Med
ISSN 2518-3389 (Print) |ISSN 2518-3397 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com/journal/sjm/home

Original Research Article

Isolated Congenital Central Hypothyroidism, A Frequently Missed Diagnosis

Nasir AM. Al -Jurayyan MD[1*], Hala G.Omer MD[2], Hadeel Z Alsarraj MD[2], Abdulrahman N. A Al -Jurayyan[3] and Sharifah DA. Al-Issa MD[4]

[1]Professor and Consultant Pediatric Endocrinologist, Endocrine Division, Department of pediatrics, King Saud University, Riyadh, Saudi Arabia
[2]Fellow, Endocrine Division, Department of pediatrics, King Saud University, Riyadh, Saudi Arabia
[3]Medical student, collage of medicine, King Saud University, Riyadh, Saudi Arabia
[4]Consultant Pediatric Endocrinologist, Endocrine Division, Department of pediatrics, King Saud University, Riyadh, Saudi Arabia

***Corresponding author:** Nasir AM. Al -Jurayyan
| **Received:** 14.05.2019 | **Accepted:** 25.05.2019 | **Published:** 30.05.2019
DOI: 10.36348/sjm.2019.v04i05.011

Abstract

Central hypothyroidism is a thyroid hormone deficiency due to a disorder of the pituitary, hypothalamus or hypothalamic -pituitary portal system, leading to diminished thyroid –stimulating hormone (TSH), thyrotropin–releasing hormone (TRH) or both. It has an estimated prevalence of approximately 1 in 100.000. It is rarely isolated and occurs more commonly in conjunction with other pituitary hormones deficiency as well as neurological signs. The clinical manifestations of isolated central hypothyroidism are usually non -specific and are often delayed or miss diagnosised. The diagnosis can be difficult and usually based on low level of free hormone (FT4) and low to normal level of thyroid –stimulating hormone (TSH). The diagnostic value of Thyrotropin –releasing hormone (TRH) test has been evaluated in such situation. The screening, in the majority relay on TSH measurement. In this article we describe three infants who were diagnosed with congenital isolated central hypothyroidism at the KKUH, Riyadh, Saudi Arabia during the period from January 2016 to April 2019, as pediatricans need to be aware of this rare condition to avoid diagnostic delay and to start the appropriate replacement therapy.

Keywords: Isolated, central, hypothyroidism, diagnosis, Thyroid –Stimulating hormone (TSH), Thyroxine, Thyrotropin releasing hormone (TRH) test.

INTRODUCTION

Central hypothyroidism (CH) is known as a hypothyroidism due to deficiency in thyroid-stimulating hormone (TSH) of an otherwise normal thyroid gland .It can be at the level of pituitary or hypothalamus. It is rare disorder with estimated prevalence of around 1in 100.000 individuals with equal sexes [1-4], Central hypothyroidism (CH) could be associated with other pituitary hormones due to variable etiology (Table-1), but rarely isolated and occur more commonly with other neurological symptoms and signs resulting from hypothalamic pituitary lesions [5-11]. The clinical and hormonal characteristics indicates that it can be difficult to diagnosis by using serum TSH as an initial screening test for thyroid dysfunction, the diagnosis of isolated central hypothyroidism may be delayed or even missed, as some may have normal or low TSH levels therefore both free thyroxine (FT4) and TSH should be performed concomitantly [12].

We report on three infants who were diagnosed to have congenital isolated central hypothyroidism in the pediatric endocrine service, King Khalid university hospital (KKUH), Riyadh, Saudi Arabia during the period January 2016 to April 2019.

MATERIAL AND METHODS

During the period January 2016 and April 2019, three infants were diagnosed to have congenital isolated central hypothyroidism at endocrine service of the king Khalid university hospital (KKUH), Riyadh, Saudi Arabia and constituted the population of the study. The diagnosis was based on the clinical suspicion and confirmed hormonally and radiologically.

Medical records were retrospectively reviewed and included age, sex, family history, clinical presentation, appropriate hormone performed and radiological investigations. Thyrotropin –releasing hormone (TRH) test was utilized to confirm the diagnosis.

RESULTS

Three infants were diagnosed to have isolated congenital central hypothyrodism. Two males and one

female. Their mean age at presentation was 7 months (range 3-9m), with a mean birth weight of 3 Kg (range 2.9-3.2 Kg). The clinical manifestations were non-specific, mainly failure to grow. Their mean level of FT4 was 10.9 Pmol/L range, (10.1-11.8) and TSH was 1.79 mU/L range (0.9-2.96). They have no clinical evidence of diabetes insipidus and other pituitary hormones were normal. TRH stimulation test was performed in one patient (Fig-1) and showed a hypothamic type of response. MRI of the pituitary and hypothalmic region (Fig-2) were normal. All patients were started on L-thyroxine.

Table-1: Etiology of central hypothyroidism

Genetic	1. Pituitary-specific transcription factor defects (PIT-1, PROP-1 LHX3 or HESX1) 2. Isolated TRH deficiency 3. TSH-(beta) subunit gene mutations (non-sense mutation, 29R mutation in exon 2, non-sense mutation at codon 49 [Q49X], frame-shifting, 1-base pair deletion) 4. Inactivating mutation in the TRH receptor gene 5. Biologically inactive TSH isoforms
Transient central hypothyroidism	Sick euthyroid syndrome, overreplacement of T4 in primary hypothyroidism
Tumors	1. Primary pituitary adenoma, cystic mass lesions (Rathke's cysts, arachnoidal cysts, colloid cysts and epidermoid cysts) 2. Metastatic pituitary lesions (lung [36%], breast [33%], thyroid) 3. Primary extrapituitary (primary intracranial) – craniopharygioma, meningioma, germinoma
Vascular	1. Hemorrhage, pituitary-apoplexy, subarachnoid hemorrhage 2. Ischemic – post-partum pituitary necrosis (Sheehan syndrome), shock 3. Aneurysm
Empty sella syndrome	
Inflammatory	1. Infectious – bacterial abscess, syphilis, tuberculosis, toxoplasmosis, neurobrucellosis 2. Non-infectious – sarcoidosis, granulomatous (idiopathic, secondary), lymphocytic hypophysitis, fungal disease, toxoplasmosis
Infiltrative	Hemochoromtosis, histiocytosis, lymphoma
Iatrogenic	1. Post-external radiation therapy 2. Post-pituitary surgery
Trauma (head injury)	
Drug related	GH therapy, glucocorticoids, somatostain therapy, RXR-selective ligand, bexarotene, salicylates, drugs interfering with neuro-dopaminergic system, dopamine, glue sniffing, morphine

Yamada M, and Mori M. Nat Clin Pract Endocrinol Metab [1]

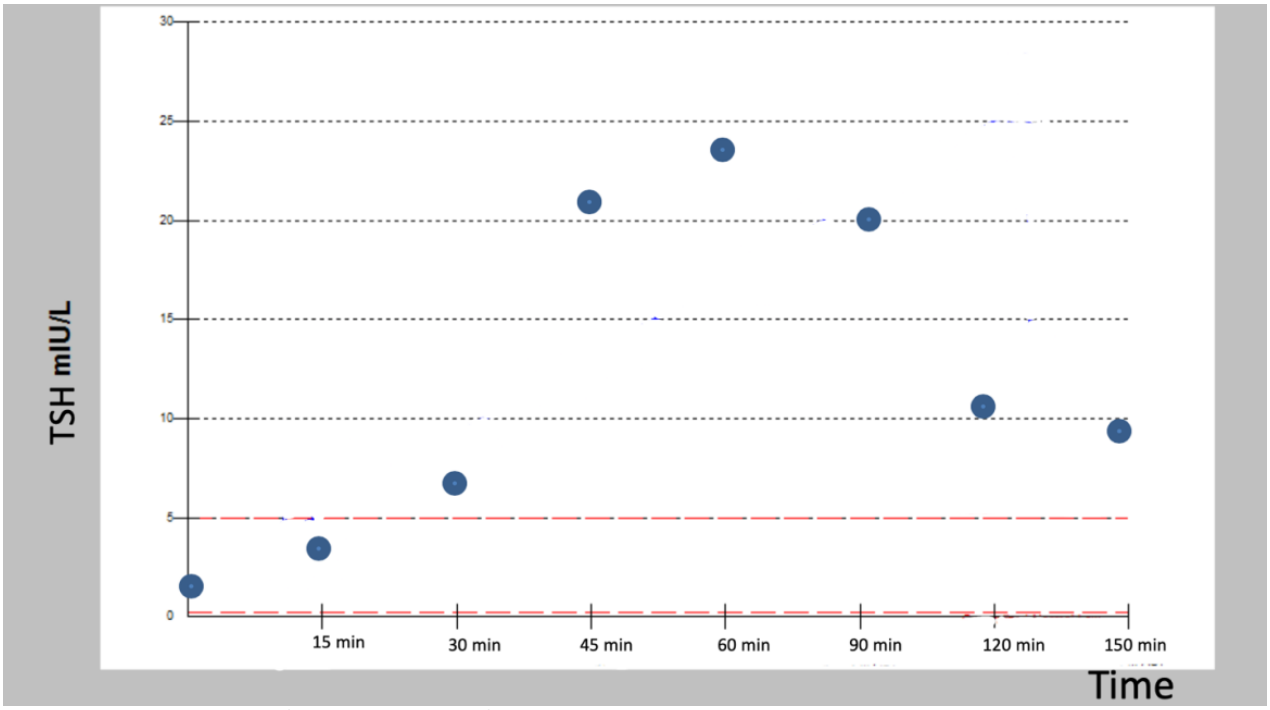

Fig-1: TRH stimulation test of a three-month old infant with isolated congenital central hypothyroidism showing hypothalamic response

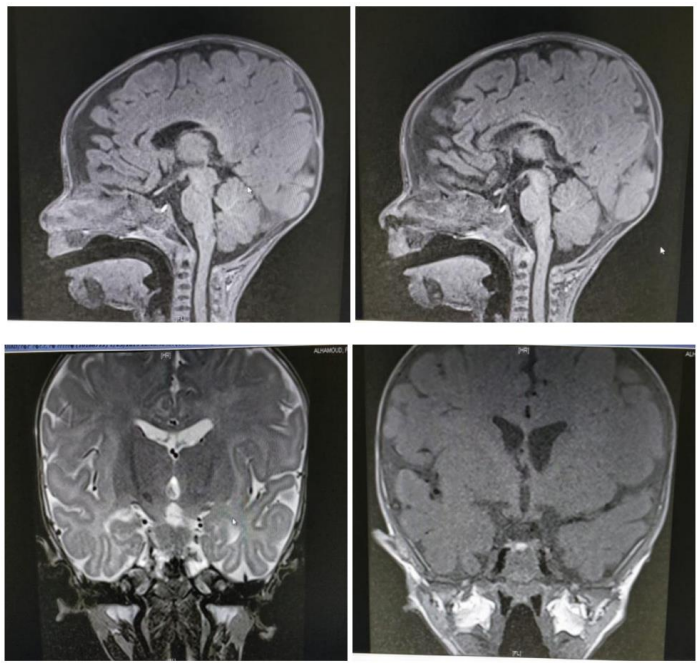

Fig-2: An MRI of the pituitary and hypothalamic region showed normal study

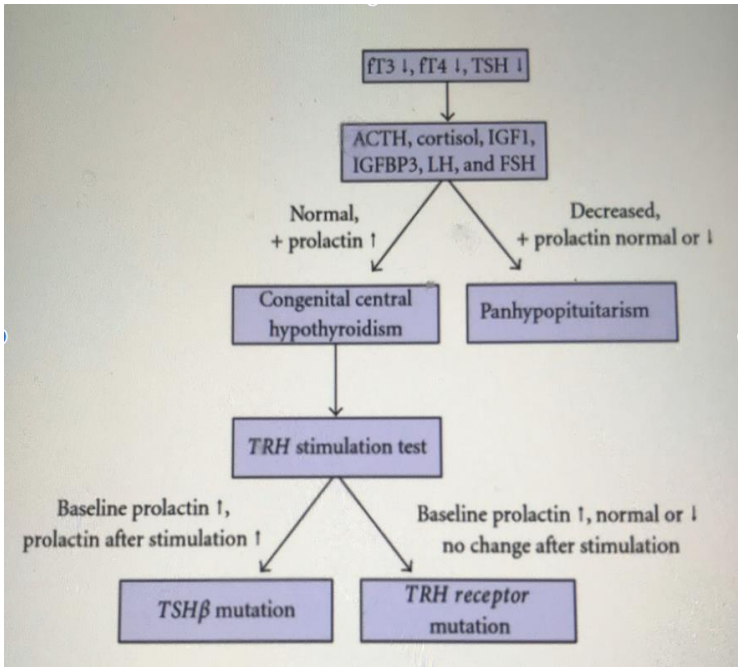

Fig-3: Schematic approach for the diagnostic pathway for congenital central hypothyroidism
Grunert *et al*., Case Rep Pedietr 2011 [15]

DISCUSSION

Congenital Central Hypothyroidism (CCH), is a very rare disease associated with insufficient thyroid hormones, as a result of Thyroid Stimulating Hormone (TSH) deficiency (either pituitary or hypothalamic origin) in spite of a normally located thyroid gland. It is commonly associated with other pituitary hormones; however, the isolated form is not that rare and seen more than expected with an estimated prevalence of 1:65,000 neonates in the Netherlands [13].

The underlying molecular basis is often undefined, but hypothalamic or pituitary pathology contributed to a quantitative deficiency in TSH synthesis or secretion. In minority of patients TSH deficiency is isolated and may occur as a result of defects in gene controlling the TSH biosynthesis pathway, e.g. mutation in the thyrotropin releasing hormones a thyroid stimulating hormones Beta subunit [14-16].

Our current patients were diagnosed to have congenital isolated central hypothyroidism based on

clinical Suspicions, which was supported by hormonal investigation and radiological studies. Unfortunately, we have no facilities to do further genetic studies.

The clinical manifestations of congenital isolated central hypothyroidism could be subtle and non- specific such as failure to thrive. unfortunately the use of TSH assay as an initial screening test for thyroid disorders, can lead into delay or even miss-diagnosed as most patient have normal low or even a slightly high serum TSH. Circulating level of FT4 remains the mainstay of diagnosis as it is usually low [17-22].

Thyrotropin- releasing hormone (TRH) stimulation test is of a value. Administration of TRH to a normal subject produces a consistent rise in serum TSH level, with a peak value is seen at 15 – 30 min, which decreases at 60min. Many patients of central hypothyroidism show either blunted or delay pattern .A delayed response of TSH to TRH is a characteristic finding of central hypothyroidism of hypothalamic origin, in contrast to the blunted response in pituitary disorders [23-25].

A magnetic- Resonance Imaging (MRI) of the hypothalamic- pituitary region should be carried out in suspected individuals.

The following (Fig-3) schematic approach has been suggested to help in minimizing the diagnostic delay in patients with central hypothyroidism [15], As central hypothyroidism is not detected by TSH based newborn screening, FT4 should be analyzed, concomitantly if hypothyroidism is clinically suspected [26].

Normal levelof ACTH, cortisol, IGF-1, IGFBP3, LH, FSH and prolactin can be of a help in diagnosis. Furthermore, a TRH stimulation test can differentiate central hypothyroidism from other types of hypothyroidism, a defective TRH receptor will neither stimulate TSH, nor prolactin However, a TSHB stimulate mutation, prolactin levels will be normal or might be Increase after TRH stimulation proving normal function of TRH receptors. TSH levels remains low.

Treatment strategies are differed in congenital hypothyroidism (CH) with neonatal to childhood onset. Normal infants and children have higher free L-thyroxin (FT_4) levels. Therefore, higher L-thyroxin doses are recommended, and treatment should be started at a full replacement doses at least in cases with neonatal onset in order to promptly protect neurological development. Recent evidence recommendsto initiate treatment with a higher doses of L-thyroxin and to adequate doses on the basis of FT4 assessment frequently. The target range should be that observed in normal children progressively lower doses are required in infancy and childhood [28-30]

CONCLUSION

The present study and earlier reports demonstrate that congenital Isolated Central Hypothyroidism may not be that very rare.

Furthermore, Studies with genetic testing and other appropriate hormone and radiological studies might be necessary for evaluation of patients with congenital Isolated Central Hypothyroidism in the future, as it might help to ascertain the extent nature of the disorder. Furthermore, pediatrician need to be aware of these issues to avoid diagnostic delay.

ACKNOWLEDGEMENT

The authors would like to express their thanks and appreciations to Mr. Ibrahim N AL-Jurayyan for his great help in preparing this manuscript.

Conflict of Interest

The authors have no conflict of interest to declare.

Funding

The authors did not receive any funding.

REFERENCES

1. Yamada, M., & Mori, M. (2008). Mechanisms related to the pathophysiology and management of central hypothyroidism. *Nature Reviews Endocrinology*, *4*(12), 683-694.
2. García, M., Fernández, A., & Moreno, J. C. (2014). Central hypothyroidism in children. In *Paediatric Thyroidology* (Vol. 26, pp. 79-107). Karger Publishers.
3. Gupta, V., & Lee, M. (2011). Central hypothyroidism. *Indian Journal Endocrine Metab*, 18;599-106.
4. Beck-Peccoz, P., Rodari, G., Giavoli, C., & Lania, A. (2017). Central hypothyroidism—a neglected thyroid disorder. *Nature Reviews Endocrinology*, *13*(10), 588-598.
5. Haugen, B. R. (2009). Drugs that suppress TSH or cause central hypothyroidism. *Best Practice & Research Clinical Endocrinology & Metabolism*, *23*(6), 793-800.
6. Einarsdottir, M. J., Olafsson, E., & Sigurjonsdottir, H. A. (2019). Antiepileptic drugs are associated with central hypothyroidism. *Acta Neurologica Scandinavica*, *139*(1), 64-69.
7. Constine, L. S., Woolf, P. D., Cann, D., Mick, G., McCormick, K., Raubertas, R. F., & Rubin, P. (1993). Hypothalamic-pituitary dysfunction after radiation for brain tumors. *New England Journal of Medicine*, *328*(2), 87-94.
8. Astapova, I., Vella, K. R., Ramadoss, P., Holtz, K. A., Rodwin, B. A., Liao, X. H., ... & Hollenberg, A. N. (2011). The nuclear receptor corepressor (NCoR) controls thyroid hormone sensitivity and

the set point of the hypothalamic-pituitary-thyroid axis. *Molecular endocrinology*, *25*(2), 212-224.

9. Nakamura, A., Bak, B., Silander, T. L., Lam, J., Hotsubo, T., Yorifuji, T., ... & Tajima, T. (2013). Three novel IGSF1 mutations in four Japanese patients with X-linked congenital central hypothyroidism. *The Journal of Clinical Endocrinology & Metabolism*, *98*(10), E1682-E1691.
10. Alafif, M. M., Aljaid, S. S., & Al-Agha, A. E. (2015). Case Report: Central Diabetes Insipidus, Central Hypothyroidism, Renal Tubular Acidosis and Dandy-Walker Syndrome: New Associations. *Annals of medical and health sciences research*, *5*(2), 145-147.
11. Fukuoka, H. (2015). Hypothyrdism *Endocrinology* and *Metabolism Clinics* of *North America*, 44;143-149.
12. Vijaya Sarathi, H. A., Bandgar, T., & Shah, N. S. (2010). Delayed recognition of central hypothyroidism in a neonate born to thyrotoxic mother. *Indian pediatrics*, *47*(9), 795-796.
13. Schoenmakers, N., Alatzoglou, K. S., Chatterjee, V. K., & Dattani, M. T. (2015). Recent advances in central congenital hypothyroidism. *Journal of Endocrinology*, *227*(3), R51-R71.
14. McDermott, M. T., Haugen, B. R., Black, J. N., Wood, W. M., Gordon, D. F., & Ridgway, E. C. (2002). Congenital Isolated Central Hypothyroidism Caused by a" Hot Spot" Mutation in the Thyrotropin-β Gene. *Thyroid*, *12*(12), 1141-1146.
15. Grünert, S. C., Schmidts, M., Pohlenz, J., Kopp, M. V., Uhl, M., & Schwab, K. O. (2011). Congenital central hypothyroidism due to a homozygous mutation in the TSHβ subunit gene. *Case reports in pediatrics*, *2011*.
16. Bondanelli, M., Ambrosio, M. R., Zatelli, M. C., De Marinis, L., & degli Uberti, E. C. (2005). Hypopituitarism after traumatic brain injury. *European Journal of Endocrinology*, *152*(5), 679-691.
17. Zwaveling-Soonawala, N., van Trotsenburg, A. P., & Verkerk, P. H. (2015). The severity of congenital hypothyroidism of central origin should not be underestimated. *The Journal of Clinical Endocrinology & Metabolism*, *100*(2), E297-E300.
18. Wassner, A. J., Cohen, L. E., Hechter, E., & Dauber, A. (2013). Isolated central hypothyroidism in young siblings as a manifestation of PROP1 deficiency: clinical impact of whole exome sequencing. *Hormone research in paediatrics*, *79*(6), 379-386.
19. Alexopoulou, O., Beguin, C., De Nayer, P., & Maiter, D. (2004). Clinical and hormonal characteristics of central hypothyroidism at diagnosis and during follow-up in adult patients. *European Journal of Endocrinology*, *150*(1), 1-8.
20. Rose, S. R. (1995). Isolated central hypothyroidism in short stature. *Pediatric research*, *38*(6), 967-973.
21. Bin-Abbas, B., Al-Mulhim, A., & Al-Ashwal, A. (2002). Wolcott-Rallison syndrome in two siblings with isolated central hypothyroidism. *American journal of medical genetics*, *111*(2), 187-190.
22. Price, A., & Weetman, A. P. (2001). Screening for central hypothyroidism is unjustified. *Bmj*, *322*(7289), 798-800.
23. Mehta, A., Hindmarsh, P. C., Stanhope, R. G., Brain, C. E., Preece, M. A., & Dattani, M. T. (2003). Is the thyrotropin-releasing hormone test necessary in the diagnosis of central hypothyroidism in children. *The Journal of Clinical Endocrinology & Metabolism*, *88*(12), 5696-5703.
24. Van Tijn, D. A., de Vijlder, J. J., & Vulsma, T. (2008). Role of the thyrotropin-releasing hormone stimulation test in diagnosis of congenital central hypothyroidism in infants. *The Journal of Clinical Endocrinology & Metabolism*, *93*(2), 410-419.
25. Atmaca, H., Tanriverdi, F., Gokce, C., Unluhizarci, K., & Kelestimur, F. (2007). Do we still need the TRH stimulation test?. *Thyroid*, *17*(6), 529-533.
26. Connelly, K. J., Pierce, M. J., Hanna, C., & LaFranchi, S. H. (2017). Detecting congenital central hypothyroidism by newborn screening: difficulty in distinguishing from congenital thyroxine-binding globulin deficiency. *Hormone research in paediatrics*, *88*(5), 331-338.
27. Persani, L. (2012). Central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges. *The Journal of Clinical Endocrinology & Metabolism*, *97*(9), 3068-3078.
28. Carrozza, V., Csako, G., Yanovski, J. A., Skarulis, M. C., Nieman, L., Wesley, R., & Pucino, F. (1999). Levothyroxine replacement therapy in central hypothyroidism: a practice report. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *19*(3), 349-355.
29. Baloch, Z., Carayon, P., Conte-Devolx, B., Demers, L. M., Feldt-Rasmussen, U., Henry, J. F., ... & Smyth, P. P. (2003). Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid: official journal of the American Thyroid Association*, *13*(1), 3.
30. Ferretti, E., Persani, L., Jaffrain-Rea, M. L., Giambona, S., Tamburrano, G., & Beck-Peccoz, P. (1999). Evaluation of the adequacy of levothyroxine replacement therapy in patients with central hypothyroidism. *The Journal of Clinical Endocrinology & Metabolism*, *84*(3), 924-929.