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Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency

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Keywords
Growth hormone · Insulin-like growth factor-I · Children · Treatment · Guidelines

Abstract
Background/Aims: On behalf of the Drug and Therapeutics, and Ethics Committees of the Pediatric Endocrine Society, we sought to update the guidelines published in 2003 on the use of growth hormone (GH). Because idiopathic short stature (ISS) remains a controversial indication, and diagnostic challenges often blur the distinction between ISS, GH deficiency (GHD), and primary IGF-I deficiency (PIGFD), we focused on these three diagnoses, thereby adding recombinant IGF-I therapy to the GH guidelines for the first time. Methods: This guideline was developed following the GRADE approach (Grading of Recommendations, Assessment, Development, and Evaluation). Results: This guideline provides recommendations for the clinical management of children and adolescents with growth failure from GHD, ISS, or PIGFD using the best available evidence. Conclusion: The taskforce suggests that the recommendations be applied in clinical practice with consideration of the evolving literature and the risks and benefits to each individual patient. In many instances, careful review highlights areas that need further research.

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ΟΔΗΓΙΕΣ ΓΙΑ ΤΗ ΧΟΡΗΓΗΣΗ ΑΥΞΗΤΙΚΗΣ ΟΡΜΟΝΗΣ ΚΑΙ ΙΝΣΟΥΛΙΝΟΜΟΡΦΟΥ ΠΑΡΑΓΟΝΤΑ-Ι ΓΙΑ ΑΣΘΕΝΕΙΣ ΜΕ ΑΝΕΠΑΡΚΕΙΑ ΑΥΞΗΤΙΚΗΣ ΟΡΜΟΝΗΣ, ΙΔΙΟΠΑΘΕΣ ΚΟΝΤΟ ΑΝΑΣΤΗΜΑ ΚΑΙ ΠΡΩΤΟΠΑΘΗ ΑΝΕΠΑΡΚΕΙΑ IGF-I

Ισχυρή σύσταση: Θεραπεία με αυξητική ορμόνη για επίτευξη φυσιολογικού αναστήματος ενήλικα σε άτομα με ανεπάρκεια αυξητικής ορμόνης.

Δεν συνιστούν δοκιμασίες πρόκλησης σε άτομα που έχουν χαμηλό ανάστημα και χαμηλό ρυθμό, μορφολογικές αλλοιώσεις της υπόφυσης υποθαλάμου, ιστορικό ακτινοβολίας και ανεπάρκεια μιας υποφυσιακής ορμόνης.

Στις υπόλοιπες περιπτώσεις πρέπει να γίνονται δοκιμασίες πρόκλησης. Η διάγνωση δεν τίθεται μόνο βασιζόμενη στις δοκιμασίες πρόκλησης. Προσοχή στα υπέρβαρα και παχύσαρκα παιδιά όπου είναι πιθανόν να έχουμε ψευδώς χαμηλές τιμές αυξητικής ορμόνης.

Συνιστάται να γίνεται priming σε αγόρια ηλικίας μεγαλύτερης των 11 χρόνων και σε κορίτσια ηλικίας μεγαλύτερης των 10 χρόνων με χορήγηση β-estradiol (όχι ethinyl estradiol) σε αγόρια και κορίτσια για 2 ημέρες πριν την δοκιμασία σε δόσεις: 1 mg για βάρος < 20 kg και 2mg για βάρος> 20 kg.

Η δόση της hrGH υπολογίζεται με βάση το βάρος (0,1-0,24 mg/kg/εβδομάδα) και όχι την IGF-I . Η IGF-I πρέπει να παρακολουθείται για έλεγχο της ανταπόκρισης και για ασφάλεια δεν πρέπει αν υπερβαίνει τα ανώτερα φυσιολογικά για το φύλο, την ηλικία και το στάδιο εφηβείας. Δεν συνιστάται αύξηση δόσης στην εφηβεία.

Σχετικά με την ασφάλεια της αυξητικής ορμόνης συστήνουν την ενημέρωση των γονέων για την πιθανότητα αυξημένης ενδοκράνιας πίεσης, υπεξάρθρημα κεφαλής μηριαίου και εξέλιξης της σκολίωσης. Κατά τη διάρκεια της θεραπείας συνιστάται έλεγχος με ιστορικό και κλινική εξέταση για αυξημένη ενδοκράνια πίεση και σκολίωση. Επίσης, συνιστάται έλεγχος για θυρεοειδική και επινεφριδιακή ανεπάρκεια. Συστήνεται παράλληλα να συζητείται η παρακολούθηση των επιπέδων του σακχάρου αίματος μόνο σε ασθενείς αυξημένου κινδύνου.

Σε ασθενείς που έχουν ιστορικό νεοπλασίας συνιστάται η απόφαση για την έναρξη θεραπείας να συζητείται με τον ογκολόγο, καθώς επίσης να συζητώνται τα νέα δεδομένα σχετικά με την πιθανότητα εμφάνισης δεύτερης νεοπλασίας. Πρέπει να μεσολαβούν τουλάχιστον 12 μήνες από την ολοκλήρωση της θεραπείας.

Στην περίπτωση που ο ασθενής φέρει άλλη διάγνωση που αυξάνει το κίνδυνο κακοήθειας, όπως σύνδρομο Down, σ. Fanconi, νευροϊνωμάτωση, σ. Noonan, σ. Blackfan-Diamond, σ. Bloom, συνιστάται να ενημερώνονται οι γονείς σχετικά με το ότι δεν υπάρχουν επαρκή δεδομένα για το αν η αυξητική ορμόνη αυξάνει τον κίνδυνο εμφάνισης νεοπλασίας.

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Brain Magnetic Resonance Imaging as First-Line Investigation for Growth Hormone Deficiency Diagnosis in Early Childhood

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Key Words

Growth hormone deficiency diagnosis · Pituitary · Magnetic resonance imaging · Childhood · Infancy

Abstract

Background/Aims: The diagnosis of growth hormone (GH) deficiency (GHD) in infancy and early childhood is not straightforward. GH stimulation tests are unsafe and unreliable in infants, and normative data are lacking. This study aims to investigate whether brain magnetic resonance imaging (MRI) may replace GH stimulation tests in the diagnosis of GHD in children younger than 4 years. ***Methods:*** We examined a retrospective cohort, with longitudinal follow-up, of 68 children consecutively diagnosed with GHD before the age of 4 years. The prevalence of hypothalamic-pituitary (HP) alterations at MRI and the associations with age and either isolated GHD (IGHD) or multiple pituitary hormone deficiency (MPHD) were assessed. ***Results:*** The prevalences of IGHD and MPHD were 54.4 and 45.6%, respectively. In the first group, brain MRI showed abnormalities in 83.8%: isolated pituitary hypoplasia in 48.7% and complex defects in 35.1%. In patients with MPHD, MRI showed complex alterations in 100%. All children younger than 24 months showed HP MRI abnormalities, regardless of the diagnosis. Complex defects were found in 94% of patients younger than 12 months and in 75% of patients between 13 and 24 months. ***Conclusion:*** Our data suggest that brain MRI may represent the first-line investigation for diagnosing GHD in infancy and early childhood.

Introduction

Children with congenital hypopituitarism may present at birth with a wide range of nonspecific symptoms including hypoglycemia, micropenis and prolonged conjugated hyperbilirubinemia [1–5]. The association of dysmorphic features, such as midline defects and craniofacial abnormalities, strongly suggests hypothalamic-pituitary (HP) alterations, which are frequently revealed by magnetic resonance imaging (MRI) [1, 2, 5, 6]. Congenital hypopituitarism manifests as isolated or multiple hormone deficiency, with growth hormone (GH) deficiency

V.P. and S.P. contributed equally to this work.

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Η ΧΡΗΣΙΜΟΤΗΤΑ ΤΗΣ ΜΑΓΝΗΤΙΚΗΣ ΤΟΜΟΓΡΑΦΙΑΣ ΓΙΑ ΤΗ ΔΙΑΓΝΩΣΗ ΤΗΣ ΣΥΓΓΕΝΟΥΣ ΑΝΕΠΑΡΚΕΙΑΣ ΑΥΞΗΤΙΚΗΣ ΟΡΜΟΝΗΣ.

Αναδρομική μελέτη 68 ασθενών (43 αγόρια) που παρακολουθούνταν σε τρία τριτοβάθμια κέντρα Παιδιατρικής Ενδοκρινολογίας στη Ρώμη και είχαν διαγωσθεί με ανεπάρκεια αυξητικής ορμόνης σε ηλικία μικρότερη των 4 χρόνων. Από αυτά 54,4% είχαν μεμονωμένη ανεπάρκεια αυξητικής ορμόνης ενώ 45,6% είχαν πολλαπλή υποφυσιακή ανεπάρκεια. Παθολογικά ευρήματα στην μαγννητική τομογραφία είχαν το 92,1% των ασθενών. Στο διάγραμμα φαίνεται το είδος της βλάβης ανά διάγνωση και ηλικιακή ομάδα.

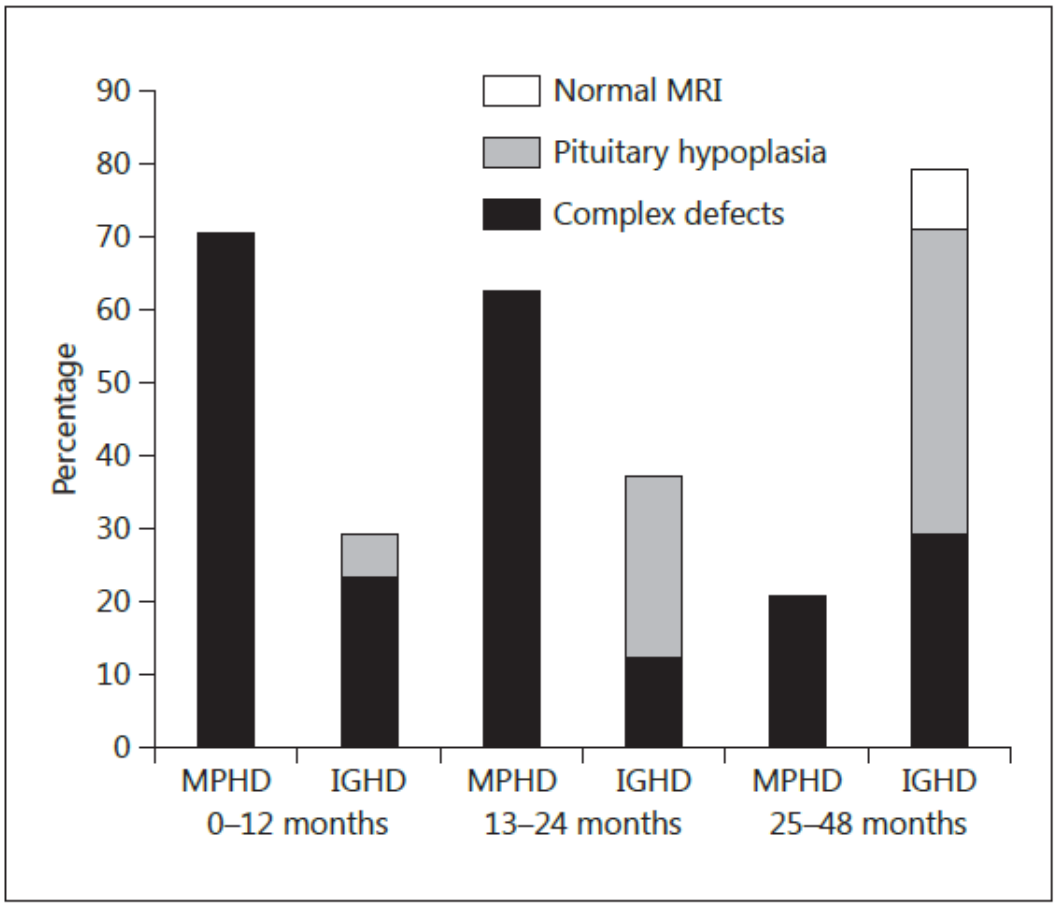

Fig. 1. Age distribution of the different MRI findings in children with either IGHD or MPHD.

Λαμβάνοντας υπόψη ότι δεν υπάρχει consensus για τη διάγνωση της ανεπάρκειας της αυξητικής ομάδας ειδικά για τις μικρές ηλικίες, και το γεγονός ότι η αξιοπιστία των διαγνωστικών δοκιμασιών είναι σχετικά χαμηλή οι συγγραφείς προτείνουν την μαγνητική τομογραφία υπόφυσης - υποθαλάμου ως δοκιμασία πρώτης επιλογής, εφόσον υπάρχει σοβαρή υποψία για ανεπάρκεια αυξητικής ορμόνης,για τη ηλικιακή ομάδα μέχρι 4 χρόνων.

Risk of Neoplasia in Pediatric Patients Receiving Growth Hormone Therapy—A Report From the Pediatric Endocrine Society Drug and Therapeutics Committee

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Context: GH and IGF-1 have been shown to affect tumor growth in vitro and in some animal models. This report summarizes the available evidence on whether GH therapy in childhood is associated with an increased risk of neoplasia during treatment or after treatment is completed.

Evidence Acquisition: A PubMed search conducted through February 2014 retrieved original articles written in English addressing GH therapy and neoplasia risk. Subsequent searches were done to include additional relevant publications.

Evidence Synthesis: In children without prior cancer or known risk factors for developing cancer, the clinical evidence does not affirm an association between GH therapy during childhood and neoplasia. GH therapy has not been reported to increase the risk for neoplasia in this population, although most of these data are derived from postmarketing surveillance studies lacking rigorous controls. In patients who are at higher risk for developing cancer, current evidence is insufficient to conclude whether or not GH further increases cancer risk. GH treatment of pediatric cancer survivors does not appear to increase the risk of recurrence but may increase their risk for subsequent primary neoplasms.

Conclusions: In children without known risk factors for malignancy, GH therapy can be safely administered without concerns about an increased risk for neoplasia. GH use in children with medical diagnoses predisposing them to the development of malignancies should be critically analyzed on an individual basis, and if chosen, appropriate surveillance for malignancies should be undertaken. GH can be used to treat GH-deficient childhood cancer survivors who are in remission with the understanding that GH therapy may increase their risk for second neoplasms. (*J Clin Endocrinol Metab* 100: 2192–2203, 2015)

ΚΙΝΔΥΝΟΣ ΝΕΟΠΛΑΣΙΑΣ ΣΕ ΑΣΘΕΝΕΙΣ ΠΟΥ ΘΕΡΑΠΕΎΤΗΚΑΝ ΜΕ ΑΥΞΗΤΙΚΉ ΟΡΜΟΝΗ

Έλεγχος της βιβλιογραφίας στο PUBMED μέχρι το 2014. Τα συμπεράσματα της επιτροπής είναι:

Παρά το γεγονός ότι τα μονοπάτια μετάδοσης του σήματος τόσο της αυξητικής ορμόνης όσο και της IGF-I, εμπλέκονται μηχανιστικά στη δημιουργία όγκων καθώς και στα σύνδρομα που προδιαθέτουν στη δημιουργία όγκων, τα διαθέσιμα κλινικά και επιδημιολογικά δεδομένα δεν υποστηρίζουν την αιτιολογική συσχέτιση της θεραπείας με αυξητική ορμόνη και της ανάπτυξης κακοήθων νεοπλασιών.

Η επιτροπή συνοψίζει τα ακόλουθα:

1. Γενικά η θεραπεία με αυξητική ορμόνη δεν αυξάνει τον κίνδυνο ανάπτυξης νεοπλασίας σε ένα υγιές παιδί χωρίς προηγούμενο ιστορικό κακοήθειας ή κάποια κατάσταση που να προδιαθέτει σε ανάπτυξη κακοήθειας.

2. Σε ασθενείς που έχουν προδιάθεση για ανάπτυξη νεοπλασίας λόγω γενετικού ή άλλου αιτίου, οι γονείς πρέπει να ενημερώνονται ότι δεν υπάρχουν αρκετά δεδομένα σχετικά με την επίδραση της θεραπείας με αυξητική ορμόνη. Συνιστάται στενή παρακολούθηση κατά τη διάρκεια της θεραπείας.

3. Σε ασθενείς που είχαν θεραπευθεί για κακοήθεια στην παιδική ηλικία και οι οποίοι έχουν ανεπάρκεια αυξητικής ορμόνης, οι γονείς πρέπει να ενημερώνονται ότι η θεραπεία δεν αυξάνει τον κίνδυνο υποτροπής αλλά ότι πιθανόν να υπάρχει αυξημένος κίνδυνος ανάπτυξης νέας κακοήθειας.

4. Η επιτροπή αναφέρεται μόνο στη θεραπεία κατά την παιδική ηλικία και όχι στην θεραπεία ενηλίκων.

Controversies in the diagnosis and management of growth hormone deficiency in childhood and adolescence

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ABSTRACT

Growth hormone deficiency (GHD) is a rare but important cause of short stature in childhood with a prevalence of 1 in 4000. The diagnosis is currently based on an assessment of auxology along with supporting evidence from biochemical and neuroradiological studies. There are significant controversies in the diagnosis and management of GHD. Growth hormone (GH) stimulation tests continue to play a key role in GHD diagnosis but the measured GH concentration can vary significantly with stimulation test and GH assay used, creating difficulties for diagnostic accuracy. Such issues along with the use of adjunct biochemical markers such as IGF-I and IGFBP-3 for the diagnosis of GHD, will be discussed in this review. Additionally, the treatment of GHD remains a source of much debate; there is no consensus on the best mechanism for determining the starting dose of GH in patients with GHD. Weight and prediction based models will be discussed along with different mechanisms for dose adjustment during treatment (auxology or IGF-I targeting approaches). At the end of growth and childhood treatment, many subjects diagnosed with isolated GHD re-test normal. It is not clear if this represents a form of transient GHD or a false positive diagnosis during childhood. Given the difficulties inherent in the diagnosis of GHD, an early reassessment of the diagnosis in those who respond poorly to GH is to be recommended.

INTRODUCTION

Growth hormone deficiency (GHD) is a rare disorder with a prevalence of approximately 1 in 4000 during childhood.[1] Although rare, it is an important diagnosis to make correctly—therapy with growth hormone (GH) in GHD is highly efficacious so a missed diagnosis will result in a poor outcome. Equally, a false positive diagnosis will lead to many years of daily subcutaneous injections, significant wasted expenditure (~£7500 per year) and unnecessary exposure to potential adverse effects. The diagnosis is multifaceted and includes an assessment of the patient's auxology, a biochemical assessment of the GH-IGF-I axis, and imaging of the hypothalamo-pituitary axis. Consensus guidelines on the diagnosis of GH deficiency in childhood were published in 2000 by the GH Research Society[2] (summary in box 1) and National Institute for Health and Care Excellence guidelines on the use of GH treatment were updated in 2010.[1]

GH secretion exists in a continuum from normality through to severe GH deficiency. The diagnosis of GH deficiency is often very clear in a child with multiple pituitary hormone deficiencies (MPHD) or where the child presents with severe GH deficiency (typically with peak GH <3 µg/L). Separating the group of short children with mild GH deficiency from non-GH deficient short children remains challenging. In this article we will review the data on diagnosis of GHD—which pharmacological stimulation test to use, issues with GH and IGF-I assays, requirement for priming and the effects of obesity. In addition we will also discuss how to select and adjust GH dose and identify non-responders to GH therapy.

DIAGNOSIS OF GHD

Outside the neonatal period (when a random GH measurement of <7 µg/L identifies GHD in neonates), measurement of random serum GH concentrations are of no clinical value as GH secretion is pulsatile with the majority of GH pulses occurring overnight, with very low GH concentrations between pulses. This means that provocative tests of GH secretion using physiological/pharmacological stimuli are required to test for GHD. GH stimulation tests use a defined cut-off concentration for peak GH to distinguish GHD from non-GHD subjects. The lack of any 'gold standard' test for GHD diagnosis has led to the development of somewhat arbitrary cut-off levels. Attempts have been made to optimise the cut-off concentration using auxological criteria to define GHD (predominantly height velocity) but these attempts have been hampered as other disorders can share similar auxology to GHD. When GH stimulation tests were first used in the 1960s, a peak GH concentration after stimulation of <5 µg/L was used to diagnose GHD on the basis that this concentration seemed to best identify patients with a GHD phenotype.[3] Over time, this cut-off has increased on the basis of very limited evidence to 7 µg/L and then 10 µg/L although most UK centres use a cut-off of 7 µg/L (A Chesover & M Dattani, unpublished data). Recent studies by Wagner *et al* (discussed below) have suggested a peak GH cut-off of 7 µg/L,[4] which is in line with the concentration generally used across the UK.

Variability and reproducibility in peak GH concentration with different physiological or pharmacological stimuli

The first test of GH secretion used was the insulin tolerance test. Subsequently a number of other pharmacological stimuli were identified including arginine, glucagon, clonidine, pyridostigmine, levodopa, GH releasing hormone (GHRH) and GHRH

ΔΙΧΟΓΝΩΜΙΕΣ ΣΤΗΝ ΑΝΤΙΜΕΤΩΠΙΣΗ ΠΑΙΔΙΩΝ ΚΑΙ ΕΦΗΒΩΝ ΜΕ ΑΝΕΠΑΡΚΕΙΑ ΑΥΞΗΤΙΚΗΣ ΟΡΜΟΝΗΣ

Οι συγγραφείς καταλήγουν στα ακόλουθα:

Οι θεράποντες ιατροί πρέπει να είναι εξοικειωμένοι με τις μεθόδους που χρησιμοποιούνται στο εργαστήριο για τον προσδιορισμό της αυξητικής ορμόνης, της IGF-I και της IGFBP3.

Εάν δεν υπάρχουν τοπικά κριτήρια για τις δοκιμασίες πρόκλησης, συνιστάται να χρησιμοποιούνται τα κριτήρια από την παρακάτω δημοσίευση:

Wagner IV, Paetzold C, Gausche R, *et al*. Clinical evidence-based cutoff limits for GH stimulation tests in children with a backup of results with reference to mass spectrometry. *Eur J Endocrinol* 2014;171:389–97.

Για τη διάγνωση της ανεπάρκειας ακολουθούν τις διεθνείς οδηγίες.

Σχετικά με το priming εφαρμόζουν priming σε αγόρια ηλικίας μεγαλύτερης των 9 χρόνων και κορίτσια ηλικίας μεγαλύτερης των 8 χρόνων.

Σχετικά με τη δόση υπολογίζουν τη δόση με το βάρος σώματος και όχι με τα επίπεδα της IGF-I και επισημαίνουν ότι η προσπάθεια να τηρούνται υψηλά επίπεδα IGF-I ενέχει τον κίνδυνο να υπάρχουν αρκετά υψηλά επίπεδα κατά διαστήματα.

Συστήνουν την εκτίμηση της απάντησης στη θεραπεία στην ολοκλήρωση του πρώτου χρόνου και εάν αυτή είναι μη ικανοποιητική (δηλαδή < -2.0 SDS) πρέπει να διερευνάται η πιθανότητα της μη συμμόρφωσης και εάν η συμμόρφωση είναι καλή, η αρχική διάγνωση να διερευνάται εκ νέου.

Mini Review

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Management of Fetal and Neonatal Graves' Disease

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Keywords
Hyperthyroidism · Graves' disease · Fetus · Neonates

Abstract
Fetal and neonatal autoimmune hyperthyroidism is a rare, serious but transient disorder. Early diagnosis and treatment are key objectives for an optimal prognosis and the well-being of the child. This review focuses on the management of these patients during the fetal and neonatal periods. We propose a diagnostic algorithm for high-risk pregnancies in mothers with current or past hyperthyroidism related to Graves' disease, involving repeated fetal thyroid gland assessments from 20 weeks of gestation onwards and maternal serum thyroid-stimulating hormone receptor antibody (TRAb) determination, with close monitoring if TRAb levels exceed 2 to 3 times the upper limit of the normal range. In fetuses with goiter, the main clinical issue is determining whether the cause is (1) maternal antithyroid drug (ATD) treatment that is appropriate for achieving normal maternal thyroid function but inappropriate and excessive for the fetus, resulting in hypothyroidism and necessitating a decrease in the ATD dose during pregnancy, or (2) the presence of TRAbs resulting in fetal thyroid stimulation and hyperthyroidism, requiring an increase in the maternal ATD dose. Methimazole/carbimazole treatment should be initiated as soon as possible during the neonatal period, carefully managed and maintained over a period of 1–3 months and then stopped when TRAb is no longer detectable in serum.

Introduction

Neonatal autoimmune hyperthyroidism (neonatal Graves' disease [GD]) is a rare but serious disorder that is generally transient, occurring in only about 2% of the offspring of mothers with GD. Cardiac insufficiency and mortality, intrauterine growth retardation, prematurity, craniostenosis, microcephaly, and psychomotor disabilities are the major risks in these infants, highlighting the importance of TRAb determination throughout pregnancy in women with GD and of the early diagnosis and treatment of fetal and neonatal hyperthyroidism. Antithyroid drugs (ATDs) are the treatment of choice for hyperthyroidism during gestation and the neonatal period, but their use during the teratogenic period of early pregnancy may be associated with a higher risk of birth defects and fetal hypothyroidism. Management of the mother, the fetus, and the neonate requires an experienced multidisciplinary team including adult and pediatric endocrinologists, obstetricians, and fetal radiologists.

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ΑΝΤΙΜΕΤΩΠΙΣΗ ΤΗΣ ΝΟΣΟΥ ΤΟΥ GRAVES (GD) ΣΤΟ ΕΜΒΡΥΟ ΚΑΙ ΣΤΟ ΝΕΟΓΝΟ

Ο νεογνικός αυτοάνοσος υπερθυρεοειδισμός είναι μια σπάνια, αλλά αρκετά σοβαρή κατάσταση που απαντάται στο 2 % των νεογνών των μητέρων με GD. Ενδομήτρια καθυστέρηση της ανάπτυξης, κρανιοσυνοστέωση, μικροκεφαλία, ψυχοκινητική καθυστέρηση και καρδιακή ανεπάρκεια με θάνατο είναι κάποιες από τις επιπλοκές. Κατά συνέπεια συστήνεται η μέτρηση των TRAb στην μητέρα κατά τη διάρκεια της εγκυμοσύνης και η θεραπεία με αντιθυρεοειδικά φάρμακα. Η χορήγης των φαρμάκων το πρώτο τρίμηνο είναι προβληματική διότι είναι πιθανό να οδηγήσει σε συγγενείς διαμαρτίες και συγγενή υποθυρεοειδισμό. Η αντιμετώπιση πρέπει να γίνεται από ομάδα ειδικών που περιλαμβάνει παιδοενδοκρινολόγο, γυναικολόγο και ακτινολόγο εξειδικευμένο στο εμβρυικό υπερηχογράφημα.

Οι μητέρες που έχουν ιστορικό GD πρέπει να παρακολουθούνται συστηματικά με μέτρηση των TRAb μετά την 20^{η} εβδομάδα ανεξάρτητα με το αν έχουν υποβληθεί σε θυρεοειδεκτομή ή έχουν θεραπευτεί με ραδιενεργό ιώδιο και ανεξάρτητα από το εάν είναι κλινικά ευθυρεοειδικές, όπως αυτό φαίνεται και στο παρακάτω διάγραμμα.

Εάν τα TRAbs είναι 2-3 φορές ψηλότερα από το ανώτερο όριο, οι κυήσεις θεωρούνται υψηλού κινδύνου και χρειάζεται παρακολούθηση του εμβρύου για το μέγεθος του θυρεοειδούς και για την καρδιακή συχνότητα και ρυθμό.

Κριτήρια εμβρυικού υπερθυρεοειδισμού είναι η βρογχοκήλη με αυξημένη αιμάτωση σε ολόκληρο τον αδένα, ενώ η αυξημένη αιμάτωση μόνο περιφερικά είναι σημείο υποθυρεοειδισμού, και η προχωρημένη οστική ωρίμανση όπως αυτή διαπιστώνεται από την εμφάνιση της κεφαλής του μηριαίου πριν τις 32 εβδομάδες κύησης σε αντίθεση με την καθυστερημένη οστική ωρίμανση δηλαδή την μη εμφάνιση της κεφαλής του μηριαίου μετά τις 32 εβδομάδες κύησης που οφείλεται σε υποθυρεοειδισμό.

Εάν διαπιστώνεται βρογχοκήλη με αυξημένη αιμάτωση και εμβρυική ταχυκαρδία πρέπει να χορηγείται θεραπεία με αντιθυρεοειδικά φάρμακα στη μητέρα.

Ο αυτοάνοσος νεογνικός υπερθυρεοειδισμός πρέπει να διαφοροποιείται από τον ιδιαίτερα σπάνιο μη αυτοάνοσο που οφείλεται σε ενεργοποιητικές μεταλλάξεις του υποδοχέα της TSH ή στο σύνδρομο McCune Albright.

Εάν τα TRAbs είναι υψηλότερα των 5 πρέπει να γίνονται μετρήσεις TSH, fT4 και T3 τις ημέρες 3, 5, 7, 10 και 15. Το νεογνό πρέπει να εξετάζεται προσεκτικά για συγγενείς διαμαρτίες και για ταχυκαρδία, θερμοκρασία. Συνιστάται νοσηλεία την πρώτη εβδομάδα της ζωής.

Εάν οι τιμές των ορμονών είναι υψηλές συνιστάται να αρχίζει θεραπεία με μεθιμαζόλη 0.5-1,0 mg/kg την ημέρα διαιρεμένο σε 2-3 δόσεις. Προπρανολόλη 2 mg/kg διαιρεμένο σε 3 δόσεις. Η δόση της μεθιμαζόλης αναπροσαρμόζεται και η προπρανολόλη διακόπτεται όταν η τιμή της

fT4 αποκαθίσταται εντός των φυσιολογικών. Η θεραπεία διακόπτεται όταν τα TRAbs αρνητικοποιούνται, συνήθως σε ηλικία 2-3 μηνών.(Πίνακας)

Table 1. Management for neonates with autoimmune hyperthyroidism

Determine TRAb in cord blood: high risk of neonatal hyperthyroidism if TRAb >5 IU/L; FT4, TSH levels: may validate the prenatal strategy but are not predictive of subsequent thyroid function
Repeated measurements of serum thyroid hormone levels during the first 2 weeks of life: days 3, 5, 7, 10, and 15
Physical examination: check for malformations
Admission to hospital for the first week of life
Initiate MMI/CMZ treatment as soon as possible: 0.5–1 mg/kg/day divided into 2–3 doses The dose should be decreased when serum FT4 levels are within the reference range
Propanolol: 2 mg/kg/day divided into 2 doses, for 2 weeks
Repeated measurement of serum TH levels weekly until stable, and then every 2 weeks
Dose titration should be preferred, but "block-and-replace" (levothyroxine) strategies may be considered in some cases
Safety of breast feeding
Treatment should be stopped when TRAb is no longer detectable in serum (1–3 months, depending on initial level)
Outcome: check for craniosynostosis, transient central hypothyroidism, long-term neuropsychological development

TRAb, thyroid-stimulating hormone receptor antibody; TSH, thyroid-stimulating hormone; TH, thyroid hormone; MMI, methimazole; CMZ, carbimazole.

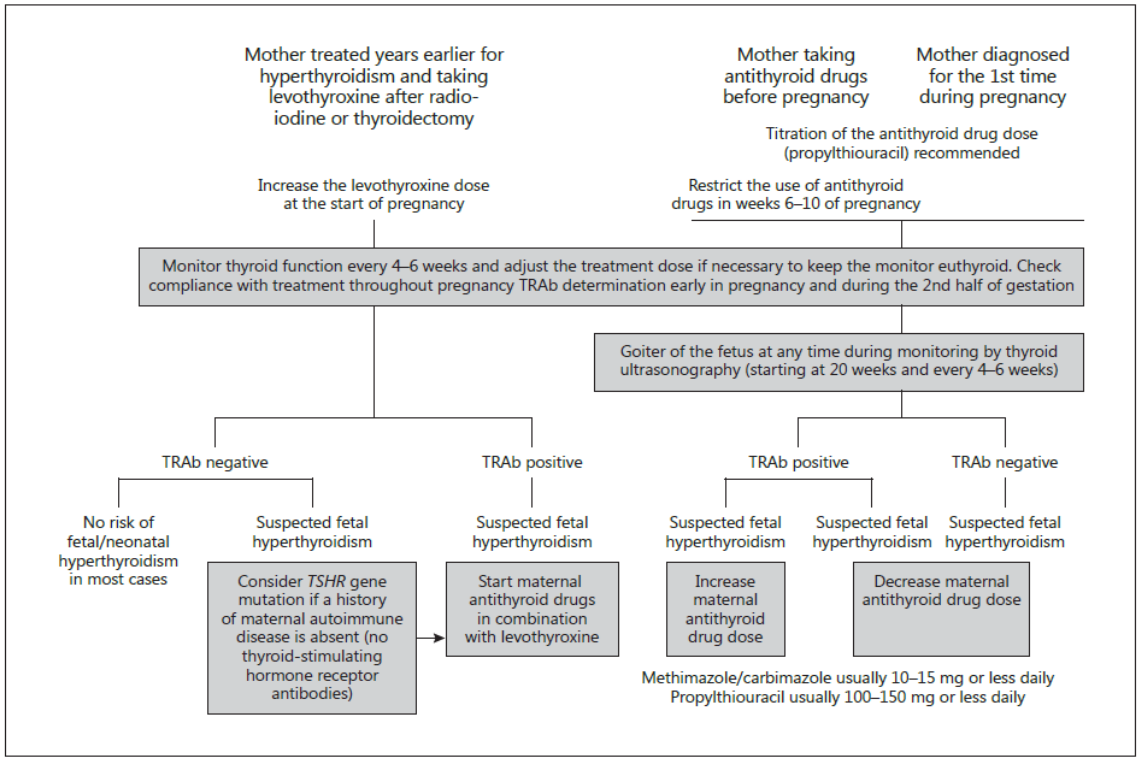

Fig. 1. Management algorithm for at-risk pregnancies in mothers with current or past hyperthyroidism mostly due to Graves' disease. After birth, check infants at risk of hyperthyroidism. Review management postpartum.

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Research Article

Thyroid-Specific Genes Expression Uncovered Age-Related Differences in Pediatric Thyroid Carcinomas

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Despite a more advanced stage of disease at presentation, a better response to radioiodine (RAI) therapy and a reduced overall mortality have been reported in pediatric differentiated thyroid cancer (DTC) in comparison to adult DTC. Few studies suggested that the better response to RAI therapy in pediatric patients might be associated with an increased expression of NIS. However, a marked heterogeneity within the pediatric group has been recognized. Children (<10 years old) usually present a more aggressive disease than adolescents (≥10–18 years old). By analyzing the expression of thyroid-specific genes in 38 sporadic pediatric tumors, we show that the expression of NIS, PDS, and TSHR was lower in children than adolescents ($P < 0.05$). A linear regression confirmed the association between NIS expression and age. Most significantly, NIS was expressed at similar levels in DTC from children and adults, whereas PDS and TSHR expression was even lower in DTC from children, compared to adolescents and adults. Our data suggest that biological behaviors of DTC in adolescents might differ from those in children and adults. Therefore, the premise that the expression of thyroid-specific genes is higher in tumors from pediatric patients than in adults is not entirely true and might be too oversimplified.

1. Introduction

Thyroid cancer is the fastest increasing cancer worldwide [1]. Although the highest incidence rates are observed in the fifth decade and it is rare in the younger population, the incidence of thyroid cancer is also increasing in children (<10 years old) and adolescents (≥10–18 years old) [2, 3]. Thyroid cancer is the 2nd most prevalent cancer in females aged 15 to 19 years [4]. Similar to adults (>18 years old), differentiated thyroid carcinomas (DTC) are the most common malignancy, with nearly 75–90% being papillary thyroid carcinoma (PTC) and the remainder follicular thyroid carcinoma (FTC) [2].

Previous studies reported significant differences in the clinical presentation and outcomes of DTC in pediatric patients (≤18 years old) compared to adults [5, 6]. Despite a more advanced stage of disease at presentation and higher rates of recurrences than adults, the overall mortality is lower [7–9]. Unlike adults, pediatric patients have a higher prevalence of pulmonary metastases, which almost always are functional [10–12]. This may explain why pediatric patients

ΕΚΦΡΑΣΗ ΤΩΝ ΘΥΡΕΟΕΙΔΙΚΩΝ ΓΟΝΙΔΙΩΝ ΣΕ ΘΥΡΕΟΕΙΔΙΚΟ ΚΑΡΚΙΝΟ ΠΑΙΔΙΚΗΣ ΗΛΙΚΙΑΣ

Ο επιπολασμός του καρκίνου του θυρεοειδούς αυξάνει συνεχώς και στην ηλικιακή ομάδα 15-18 χρ. αποτελεί τον δεύτερο σε συχνότητα καρκίνο. Ο καρκίνος του θυρεοειδούς στην παιδική ηλικία είναι συνήθως μεγαλύτερου μεγέθους και έχει συχνότερα μεταστάσεις από ότι ο καρκίνος του θυρεοειδούς που διαγιγνώσκεται στην ενήλικη ζωή. Παρ' όλα αυτά έχει καλύτερη πρόγνωση σε σύγκριση με αυτό των ενηλίκων.

Για να διερευνηθεί κατά πόσο η διαφορετική αυτή συμπεριφορά οφείλεται σε διαφοροποίηση σε γενετικό επίπεδο, ελέγχθηκε η έκφραση των NIS, TPO, Thyroglobulin (TG), PDS, TSHR σε παιδιατρικούς ασθενείς και η ανάλυση έγινε για την ηλικιακή ομάδα κάτω των 10 χρόνων και για την ηλικιακή ομάδα 10-18 χρόνων. Η έκφραση των NIS, TPO, TG, PDS, TSHR ήταν στατιστικά σημαντικά χαμηλότερη στον θυρεοειδικό καρκίνο της παιδικής ηλικίας συγκριτικά με το φυσιλογικό θυρεοειδικό ιστό. Η έκφραση των NIS, PDS και TSHR ήταν χαμηλότερη στα παιδιά σε σχέση με τους έφηβους. Επίσης, η έκφραση του mRNA του NIS και του TSHR ήταν μικρότερη στους καρκίνους με επέκταση εκτός του θυρεοειδούς αδένα. Επίσης η έκφραση του mRNA του NIS ήταν χαμηλότερη όταν υπήρχαν και πνευμονικές μεταστάσεις.

MANAGEMENT OF ENDOCRINE DISEASE

Long-term outcomes of the treatment of central precocious puberty

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Abstract

GnRH analogues (GnRHa) are the treatment of choice for central precocious puberty (CPP), with the main objective to recover the height potential compromised by the premature fusion of growth cartilages. The aim of this review was to analyze long-term effects of GnRHa on height, body weight, reproductive function, and bone mineral density (BMD) in patients with CPP, as well as the potential predictors of outcome. Because randomized controlled trials on the effectiveness and long-term outcomes of treatment are not available, only qualified conclusions about the efficacy of interventions can be drawn. GnRHa treatment appears to improve adult height in girls with CPP, especially if diagnosed before the age of 6, whereas a real benefit in terms of adult height is still controversial in patients with the onset of puberty between 6 and 8 years of age. No height benefit was shown in patients treated after 8 years. Gonadal function is promptly restored in girls after cessation of treatment, and reproductive potential appears normal in young adulthood. Data are conflicting on the long-term risk of polycystic ovarian syndrome in both treated and untreated women. Fat mass is increased at the start of treatment but normalizes thereafter, and GnRHa itself does not seem to have any long-term effect on BMI. Similarly, analogue treatment does not appear to have a negative impact on BMD. Owing to the paucity of data available, no conclusions can be drawn on the repercussions of CPP and/or its treatment on the timing of menopause and on the health of the offspring.

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Introduction

Puberty results from the reactivation of the hypothalamic–pituitary–gonadal (HPG) axis following the quiescent period occurring during childhood. It is characterized by an increase in the amplitude and frequency of the hypothalamic gonadotropin-releasing hormone (GnRH) pulses, which in turn promote follicle-stimulating hormone and luteinizing hormone secretion by the pituitary, leading to the activation of gonadal function (1).

Precocious puberty is clinically defined by the appearance of secondary sexual characteristics, i.e., Tanner stage II of breast development before the age of 8 in girls and the increase in testicular volume $\geq$4 ml before 9 years in boys (2, 3). Central precocious puberty (CPP) due to early activation of pulsatile GnRH secretion is the most common form (2). It occurs in ~1:5000–10 000 children, with a female-to-male ratio ranging from 3:1 to 23:1 (3). Females typically present with idiopathic forms, whereas in boys CPP is mostly due to organic lesions such as hypothalamic–pituitary congenital malformations, tumors, infections, infiltrative/inflammatory disorders, and iatrogenic or traumatic injuries (3). Genetic factors (mutations of KISS1, KISS1R, and MKRN3 genes (4)), secular trend, ethnicity, nutritional status, and environmental changes have all been involved in the pathogenesis of CPP (2, 3, 5), although their exact mechanisms of action remain to be elucidated.

Short stature caused by rapid advancement of skeletal maturation driven by premature exposure to sex steroids is

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ΑΠΩΤΕΡΑ ΑΠΟΤΕΛΕΣΜΑΤΑ ΤΗΣ ΘΕΡΑΠΕΙΑΣ ΤΗΣ ΚΕΝΤΡΙΚΗΣ ΠΡΩΙΜΗΣ ΗΒΗΣ

Μετα-ανάλυση στην οποία περιελήφθησαν 75 δημοσιεύσεις. Περιορισμός όλων των μελετών είναι ότι δεν υπάρχουν τυχαιοποιημένες (RCT) μελέτες.

Σχετικά με την επίδραση της θεραπείας στο τελικό ανάστημα, 20 μελέτες αφορούσαν την επίδραση στο τελικό ανάστημα. Φάνηκε ότι η πλειοψηφία των μελετών διαπίστωσε ότι οι ασθενείς έφτασαν το ύψος στόχο, ένα μικρό ποσοστό δεν έφτασε το ύψος στόχο, ενώ σε ένα πολύ μικρό ποσοστό αθενών το τελικό ανάστημα ήταν χαμηλότερο από το προβλεπόμενο πριν την θεραπεία.

Αναφορικά με τους παράγοντες που επηρεάζουν την έκβαση της θεραπείας στις περισσότερες μελέτες αναδεικνύεται η νεαρότερη ηλικία έναρξης της εφηβείας και έναρξης της θεραπείας, η μεγαλύτερη διάρκεια θεραπείας, το μικρότερο χρονικό διάστημα μεταξύ της έναρξης της εφηβείας και της έναρξης της θεραπείας, η μεγαλύτερη ανάπτυξη μετά το τέλος της θεραπείας, και η προχωρημένη οστική ηλικία κατά την έναρξη της θεραπείας επηρεάζουν ευνοικά το τελικό ανάστημα.

Μία μελέτη διαπίστωσε ότι εάν ο λόγος οστικής ηλικίας προς χρονολογική ηλικία ήταν ιδιαίτερα αυξημένος τα αποτελέσματα δεν ήταν καλά, καθώς επίσης άλλη μελέτη καταλήγει στο ότι η θεραπεία δεν είναι αποτελεσματική εάν η οστική ηλικία είναι ίση ή μεγαλύτερη των 12 χρόνων. Θετική επίδραση στο τελικό ανάστημα είχε το υψηλότερο ύψος κατά την έναρξη και κατά τη διακοπή της θεραπείας, καθώς και το υψηλότερο ανάστημα στόχος.

Σχετικά με την επίδραση στο Δείκτη Μάζας Σώματος (ΔΜΣ): Οι περισσότερες μελέτες αναφέρουν υψηλότερο Δείκτη Μάζας Σώματος κατά την έναρξη και οι περισσότερες δεν διαπίστωσαν αύξηση κατά τη διάρκεια της θεραπείας, ενώ μία διαπίστωσε αύξηση του ΔΜΣ των νορμοβαρών κοριτσιών αλλά όχι των υπέρβαρων.

Σχετικά με την αναπαραγωγική λειτουργία και την ανάπτυξη συνδρόμου πολυκυστικών ωοθηκών οι περισότερες μελέτες αναφέρουν εμμηναρχή σε ποσοστό 100 % με ελάχιστες εξαιρέσεις που αφορούσαν οργανικής αιτιολογίας πρώιμη ήβη λόγω υποθαλαμικού αμαρτώματος.

Η μέση διάρκεια από τη διακοπή της θεραπείας μέχρι την εμμηναρχή είναι 1,1 $\pm$ 0,4 χρ. Η νεαρότερη διάρκεια έναρξης της θεραπείας και η μεγαλύτερη διάρκεια θεραπείας φαίνεται να συσχετίζεται με μακρύτερο χρονικό διάστημα μέχρι την εμμηναρχή.

Όσον αφορά την ανάπτυξη συνδρόμου πολυκυστικών ωοθηκών τα δεδομένα είναι αντικρουόμενα με τις περισσότερες μελέτες να μην υποστηρίζουν τη συχέτιση της θεραπείας με την ανάπτυξη του συνδρόμου.

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Research Article

Papillary Thyroid Carcinoma Arising in Children and Adolescent Hashimoto's Thyroiditis: Ultrasonographic and Pathologic Findings

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Objectives. We compared the ultrasonography and pathology features of papillary thyroid carcinoma (PTC) in pediatric and adolescents with Hashimoto's thyroiditis (HT) with those of non-HT patients. *Materials and Methods*. Eleven patients who were surgically confirmed to have pediatric or adolescent PTC from 2006 to 2014 were included in this study. We retrospectively analyzed the preoperative ultrasonography and pathology features of PTC arising in HT and non-HT patients. *Results*. On ultrasonography, thyroid gland was lobulated and enlarged, with many scattered microcalcifications in four of five HT patients. Four of six non-HT patients had suspicious masses with calcifications. The diffuse sclerosing variant of PTC (DSVPTC) was found in three of five HT patients, but none in non-HT patients. Macroscopic or microscopic extrathyroidal extension was evident in all of the HT patients and four of the non-HT patients. Neck lymph node metastases were in all HT patients and five of non-HT patients. *Conclusions*. Three of five PTCs in pediatric and adolescent HT patients were DSVPTC, whereas all PTCs of the non-HT patients were classic type. On ultrasonography, thyroid gland was diffusely enlarged with scattered microcalcifications in four of five HT patients. All five HT cases had aggressive disease, including extrathyroidal extension and cervical lymph node metastases.

1. Introduction

Thyroid carcinoma is uncommon in children, constituting 0.5~3% of all pediatric malignancies [1–4]. Papillary thyroid carcinoma (PTC) is the most common type of pediatric and adult thyroid carcinoma [5]. Hashimoto's thyroiditis (HT) is the most common form of diffuse thyroid disease, which is characterized by diffuse lymphocytic infiltration, and affects 1.3% of children and adolescents [5–7]. Some evidence suggests that HT patients are at an increased risk of PTC compared to the general population [8–10]. However, as PTC is rare in pediatric and adolescent HT patients, the carcinoma has been poorly studied. Therefore, we compared the ultrasonography and pathology features of PTC arising in pediatric and adolescent HT, and non-HT patients.

2. Materials and Methods

2.1. Patients. Institutional Review Board approval was obtained for this retrospective study and the requirement for informed patient consent was waived.

Thirteen patients were diagnosed with pediatric or adolescent PTC in our institution from July 2006 to April 2014. Of these, this study enrolled the 11 patients who underwent surgery. Two patients were excluded: one because, although PTC was diagnosed by fine needle aspiration biopsy (FNAB) in our institution, the patient was subsequently transferred to another hospital, and the other had undergone radiofrequency ablation in another hospital before PTC was diagnosed, which likely affected the characteristics of the mass. We retrospectively analyzed the preoperative

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Congenital Hypothyroidism: Optimal Initial Dosage and Time of Initiation of Treatment: A Systematic Review

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Abstract

Context: Appropriate management of neonates, tested positive for congenital hypothyroidism (CH), in particular, the initial dosage of levothyroxine and the time of initiation of treatment is a critical issue. The aim of this study was to assess all current evidence available on the subject to ascertain the optimal initial dose and optimal initiation time of treatment for children with CH.

Evidence Acquisition: In this study, all published research related to the initiation treatment dose and the onset time of treatment in congenital hypothyroidism were reviewed. The searched electronic databases included Medline, Science direct, Scopus EMBASE, PsycINFO, Cochrane, BIOSIS and ISI Web of Knowledge. Additional searches included websites of relevant organizations, reference lists of included studies, and issues of major thyroid and pediatrics journals published within the past 35 years. Studies were included if they were written in English and investigated levothyroxine dose or timing of treatment or both, used for the treatment of children with congenital hypothyroidism.

Results: Two thousand three hundred and seventy-four articles (excluding duplicates) were retrieved from the primary search. After reviewing the titles, abstracts and full-texts of studies, eventually, 22 studies were found that met our inclusion criteria. Amongst these, 17 and 12 evaluated outcomes of different treatment doses and treatment timing, respectively. Overall, the majority of these studies emphasized the initial high dose of levothyroxine and early treatment of newborns with hypothyroidism. There were, however, some studies that disagreed with increasing levothyroxine dose at initiation of treatment.

Conclusions: Considering the results of this review, apparently there is no difference in opinion regarding the early initiation of treatment, whereas determining the optimal dose of levothyroxine for start of treatment in CH patients still remains a controversial issue, demonstrating the need for further studies, despite the fact that use of high doses can lead to rapid normalization of biochemical indices, although this may cause complications.

Keywords: Congenital Hypothyroidism, Starting Treatment Dose, Treatment Initiation Timing, Review Article

1. Context

Congenital hypothyroidism (CH), one of the most prevalent endocrine diseases, is known as a common preventable cause of mental retardation (1). Mass population screening of newborn infants for CH, first introduced in 1974, is today a routine and effective tool of timely/early diagnosis of CH, used throughout the world (2). Detection of children with CH by screening programs and treatment with levothyroxine is currently the standard method for the control of CH, a cause of mental retardation (3). Available data shows that during pregnancy very little thyroxine crosses the placenta from the mother to the fetus and most children are born without signs or symptoms of hypothyroidism (4, 5). Following diagnosis, if tested positive for CH, what is important is the early treatment of children with CH, using an appropriate initiation dose of levothyroxine sodium.

Previous studies, conducted over the past three decades earlier, show that initiation of treatment within the first two to three weeks of life resulted in both normal IQ and physical growth (6, 7). Intellectual outcomes in children with CH are affected by bone age, initial serum T4, hypothyroidism etiology, and age at which treatment is started. Those with bone ages of < 36 weeks' gestation, had the lowest T4, and were a thyroid, and those treated later than four weeks were most vulnerable to mental retardation and physical incomplete growth (8, 9).

Arvat E, Falorni A (eds): Cortisol Excess and Insufficiency.
Front Horm Res. Basel, Karger, 2016, vol 46, pp 184–195 (DOI: 10.1159/000443919)

Congenital Adrenal Hyperplasia: Unresolved Issues

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Abstract

Congenital adrenal hyperplasia (CAH) describes a family of disorders that comes from enzymatic deficiencies in cortisol production, with 21-hydroxylase deficiency causing ~90% of cases. Distinction is made between the severe classical form and milder nonclassical form of CAH. Molecular genetic analysis is used to confirm the hormonal diagnosis. A high rate of genotype-phenotype discordance has been found in 21-hydroxylase deficiency. The goal of treatment is to replace with synthetic glucocorticoids and mineralocorticoids and suppress adrenal androgen production. The treatment of patients affected with nonclassical CAH, particularly males, remains controversial. Variable synthetic glucocorticoids are used and new modes of glucocorticoid delivery are under investigation. To improve height, growth hormone and other adjuvant therapies are employed. Long-term outcomes of genital surgery using modern techniques in females affected with classical CAH continue to be investigated. Prenatal treatment with dexamethasone is available to avoid ambiguous genitalia in these females. Although studies have shown its safety to mother and fetus, prenatal treatment is still regarded as experimental. Currently, prenatal diagnosis of CAH can only be obtained through invasive methods. Recently, the detection of cell-free fetal DNA in maternal plasma has made it possible to make this diagnosis earlier and noninvasively.

Congenital adrenal hyperplasia (CAH) refers to a group of autosomal recessive disorders in which genetic enzyme deficiencies lead to impaired steroid synthesis. The production of cortisol from cholesterol occurs in the zona fasciculata of the adrenal cortex through five major enzymatic conversions. Impaired cortisol synthesis, which is common to all forms of CAH, leads to elevation of adrenocorticotropic hormone

Bourguignon J-P, Parent A-S (eds): Puberty from Bench to Clinic. Lessons for Clinical Management of Pubertal Disorders. Endocr Dev. Basel, Karger, 2016, vol 29, pp 214–229 (DOI: 10.1159/000438893)

Gonadotropin-Releasing Hormone Agonist Treatment in Sexual Precocity

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Abstract

Depot gonadotropin-releasing hormone (GnRH) analogs represent the first-line therapy in sexual precocity due to central precocious puberty. GnRH analogs desensitize the pituitary and account for the suppression of luteinizing hormone and follicle-stimulating hormone leading to a decrease of sex steroid levels. The conventional indications are central puberty starting before the age of 8 years in girls and 9 years in boys. These indications can be extended to difficult conditions with poor adult height prognosis or marked psychosocial impact. This includes children after irradiation, international adoption, and children with a physical handicap or mental disabilities. There are different formulations of depot preparations of GnRH analogs; long-acting 1- or 3-month forms are widely used in Europe and all are well tolerated with minor side effects. Overweight is often present at the onset of precocious puberty and some etiologies such as hamartomas predispose to obesity, requiring appropriate care for weight control during and after the cessation of GnRH analog treatment. Many studies have reported on the effects on adult height, which seems to be especially beneficial when treatment is started before the age of 6; however, few studies have focused on the establishment of the 1st menstruation, 1st sexual intercourse, socioprofessional outcome and subsequent fertility.

Questions about the timing of pubertal development are a frequent reason for consultation in pediatric endocrinology. It is estimated that central precocious puberty (CPP) affects 1 in 5–10,000 children, and occurs at least ten times more frequently in girls than in boys; in more than 90% of the girls, sexual precocity is idiopathic [1]. The etiologies of sexual precocity are subdivided into gonadotropin-releasing hormone (GnRH)-dependent and GnRH-independent causes, also called CPP and peripheral precocious puberty, respectively. Depot GnRH analogs represent the first line of therapy in CPP [2].

RASopathies Are Associated With Delayed Puberty; Are They Associated With Precocious Puberty Too?

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RASopathies, such as Noonan, Costello, and cardio-facio-cutaneous syndromes, are developmental disorders caused by mutations in rat sarcoma–mitogen-activated protein kinase pathway genes. Mutations that cause Noonan syndrome have been associated with delayed puberty. Here we report 4 patients with either Costello or cardio-facio-cutaneous syndrome who developed precocious puberty, suggesting complex regulation of the hypothalamic–pituitary–gonadal axis and the timing of puberty by the rat sarcoma–mitogen-activated protein kinase pathway. Additional study of the timing of puberty among patients with RASopathies is warranted to ascertain the incidence of delayed and precocious puberty in these conditions and to examine genotype–phenotype correlations, which may provide insight into pathways that regulate the timing of puberty.

Despite recent advances,[1–3] many factors that regulate timing of puberty remain elusive. Rare syndromes associated with disorders in pubertal timing provide additional opportunities to identify genetic pathways that regulate the onset of puberty. RASopathies are developmental disorders caused by heterozygous activating germline mutations in rat sarcoma–mitogen-activated protein kinase (RAS-MAPK) pathway genes.[4,5] The RAS-MAPK pathway plays a central role in signal transduction from extracellular stimuli to the intracellular environment. The pathway is activated through hormones and growth factors that bind to tyrosine kinase, G-protein coupled, or extracellular matrix receptors. Binding results in phosphorylation and activation of proteins that control cell growth, differentiation, proliferation, and apoptosis, all critical aspects of normal development.[6,7]

RASopathies include Noonan syndrome (NS), Costello syndrome (CS), and cardio-facio-cutaneous syndrome (CFCS). These syndromes have overlapping features, such as craniofacial dysmorphisms; cardiac malformations; cutaneous, musculoskeletal, and ocular abnormalities; and developmental delay.[7] The overall incidence of RASopathies is 1 in 1000 to 2500 live births. NS is the most common condition. CS and CFCS are much rarer, with unknown exact prevalence.[8]

Although delayed puberty is described as a typical, although not universal, feature of NS,[9] little has been reported about pubertal timing in CS and CFCS. Delayed puberty has been described in CS,[10–13] and isolated cases of precocious puberty have been noted anecdotally in CS[14] and CFCS.[15–17] Unfortunately, only 1 of these articles describes clinical and biochemical data related to the

abstract

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Dr van der Kaay jointly conceived the article and assisted in planning its execution, performed literature searches, and drafted the initial manuscript; Dr Levine provided medical information for 1 of the cases, critically reviewed manuscript drafts, and made detailed edits; Dr Doyle provided medical information for 1 of the cases and critically reviewed manuscript drafts; Drs Mendoza-Londono and Palmert jointly conceived the article and assisted in planning its execution, co-supervised the project, critically reviewed manuscript drafts, and made detailed edits; and all authors approved the final manuscript as submitted.

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Plasma concentrations of osteocalcin are associated with the timing of pubertal progress in boys

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Abstract

Background: Animal models have shown that the skeletal hormone osteocalcin stimulates testicular testosterone synthesis. To assess whether osteocalcin might be a useful marker to detect pubertal development disorders, we examined osteocalcin plasma concentrations in children and adolescents with and without disorders of pubertal development.

Methods: Osteocalcin concentrations were investigated in a total of 244 patients with endocrine disorders (122 males, mean age: 11.87 + 3.77 years), including patients with precocious puberty and constitutional delay of puberty.

Results: Osteocalcin concentrations were highest among adolescents with precocious puberty and advanced pubertal development (120.60 ± 45.22 ng/mL), while the concentrations were lowest among patients with constitutional delay of puberty (102.20 ± 37.13 ng/mL). Overall, osteocalcin concentrations were strongly correlated with markers of bone metabolism.

Conclusions: Although plasma osteocalcin concentrations are associated with pubertal development in boys, it does not appear to be a useful diagnostic marker for altered pubertal development.

Keywords: delayed puberty; osteocalcin; precocious puberty; pubertal development.

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Introduction

Osteocalcin is a skeletal system hormone that is secreted by osteoblasts. Accordingly, circulating concentrations of osteocalcin are positively associated with markers of bone metabolism, such as total serum alkaline phosphatase (TSAP) and parathyroid hormone (PTH) [1, 2]. During periods of growth, osteocalcin concentrations are increased in children and adolescents [3].

Osteocalcin also exhibits metabolic effects: it increases insulin sensitivity in the skeletal muscle, insulin secretion by pancreatic beta cells [4, 5] and adiponectin release by adipocytes [6]. In contrast, leptin, an adipocyte-derived hormone, has a negative effect on osteocalcin concentrations by inhibiting osteocalcin production by osteoblasts [7, 8].

Osteocalcin has recently been found to stimulate testosterone production in Leydig cells in a mouse model, thereby implying that osteocalcin plays a role not only in the pubertal growth spurt [9] but also in male pubertal development [10, 11]. Even though osteocalcin levels change during female pubertal development, no likewise influence of osteocalcin on gonadal development and hormone expression seems to exist in females [12, 13].

Therefore, we aimed to investigate whether osteocalcin concentrations are associated with pubertal stages in children and adolescents with and without disorders of pubertal development and whether this hormone might be a useful marker to detect pubertal development disorders.

Patients and methods

This study was performed at the endocrine outpatient clinic of the Children's Hospital, University of Duisburg-Essen, Germany, between

RESEARCH PAPER

Vitamin D Deficiency and Parathyroid Response in Critically-ill Children: Association with Illness Severity and Clinical Outcomes

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Objective: To determine the prevalence of vitamin D deficiency in critically ill children, and to study its association with parathyroid response, severity of illness and clinical outcomes.

Design: Prospective observational study.

Setting: Medical Pediatric Intensive Care Unit of a tertiary care centre of Northern India.

Participants: 154 children in-patients: August 2011-January 2013.

Main outcome measures: Vitamin D deficient children were (serum 25-hydroxy vitamin D <20 µg/mL) divided into "parathyroid-responder" [serum parathyroid hormone >65 pg/mL with 25(OH)D<20 µg/mL and/or calcium corrected for albumin <8.5 mg/dL] and "non parathyroid-responder." Illness severity was assessed by Pediatric Index of Mortality-2 (PIM-2) score at admission. Biochemical parameters, illness severity scores and clinical outcomes were compared between parathyroid-responders and non-parathyroid-responders.

Results: Vitamin D deficiency and hypocalcemia were observed in 125 (83.1%) and 91 (59%) children, respectively at admission. There were no differences in illness severity score at admission, mortality rate and length of stay between vitamin D-deficient children and 19.8% of non-vitamin D-deficient children. Among Vitamin D-deficient children, parathyroid-responders had higher PIM-2 score at admission compared to non-parathyroid-responder [12.8 (7.4,20.6) *vs.* 6.5 (2.5,12.2), *P*=0.01]. However, there were no differences in other clinical outcomes between two groups.

Conclusion: Critically ill children have high prevalence of vitamin D deficiency. Parathyroid gland response secondary to hypocalcemia or vitamin D defiency is impaired in critical illness.

Keywords: *Calcium, Illness severity, Outcome.*

The pleiotropic action of vitamin D plays a central role in the critical illness pathophysiology. Vitamin D receptor is found in B and T lymphocytes, bone marrow and cardiac cells, and there is growing evidence regarding its cardio-protective, immunomodulatory and antimicrobial properties [1]. Studies have documented higher prevalence of vitamin D deficiency in critical care settings [2-6]. Whether this deficiency is associated with severity of illness or other clinical outcomes is unclear [10].

We hypothesized that there is impairment in the Calcium—Parathyroid hormone (PTH)–Vitamin D axis due to critical illness. Assessing vitamin D deficiency in terms of PTH response and its association with illness severity and clinical outcomes is necessary to get insight for further interventional studies for optimizing the management of Vitamin D deficiency, particularly in the setting where vitamin D deficiency is highly prevalent even in healthy children. We, therefore, conducted this study to determine the prevalence of Vitamin D deficiency and characterize its relation with calcium and PTH, and assess the outcome considering type of parathyroid response in vitamin D-deficient children.

Accompanying Editorial: Pages 475-476.

METHODS

This was a prospective cohort study conducted in Pediatric Intensive Care Unit (PICU) of All India Institute of Medical Sciences, New Delhi, India, and was a secondary objective of data collected as a part of 'Hypophosphatemia in Pediatric Critical Illness' study by the same group. In this study, all the children aged between 1 month and 15 years were eligible for inclusion. Exclusion criteria were: known parathyroid disease, rickets, renal tubular acidosis, chronic kidney disease (CKD) diagnosis of acute kidney injury (AKI) at admission. Children requiring readmission and those who died within 24 hours were also excluded. Ethical approval was obtained from Institutional ethics committee. Parents of the children fulfilling the criteria were approached for the written informed consent for the participation of the child in the study.