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RESEARCH ARTICLE

TRANSIENT FAMILIAL CONGENITAL HYPOTHYROIDISM: ABOUT A SIBLING OF THREE

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Abstract

Introduction: Congenitalhypothyroidismis one of the mostcommonpreventable causes of intellectualdisability. It isclassifiedinto permanent and transient. The transientdisorderrefers to atemporarydeficiency of thyroid hormones at birth but thenrecovering to normal thyroïd hormone production.Wewillpresent a case of congenitalhypothyroidism in a sibling of three.

Case Report: Symptomatologyseems to date back to the age of 2 months in the first two siblings for whichtheywerehospitalized in pediatrics for hypotonia and macroglossiaassociated to anemia.Contrastingwith the youngest sibling whowasscreened at day 7 of life .Biologicalfindingsrevealedhypothyroidism.Supplemented by ultrasoundshowing a normal thyroid volume, whilethyroidscintigraphyrevealed a moderatelyreduced fixation.Theywere all put on Levothyroxin. However, wenoted a spontaneousimprovement in theyoungestbrotherleading to cessation of hormone replacement therapy at the age of 5.

Discussion: Whilethyroiddysgenesisremains the mostcommon cause of congenitalhypothyroïdism, theincidence of dyshormonogenesis has been increasing over the last few decades.Transienthypothyroidismmaybecaused by mutations in the genesencodingessentialy forDUOX2/DUOXA2 suspected in our sibling due to the transientcaracter in youngerbrother.However, mutations in pendrine, sodium iodinesymporter, thyroidperoxidade, thyroglobulingenes are oftenassoxiatedwithgoiter and severe permanent hypothyroidism.Finally, new born screening and effective treatmentis a major achievement in preventivemedicine.

Introduction:-

Congenitalhypothyroidism (CH) isdefined as thyroid hormone deficiencypresent at birth. Thyroid hormone (TH) action for neurodevelopmentislimited to a specific time window, and even a short period of deficiency of TH can cause irreversiblebrain damage, making CH one of the mostcommonpreventable causes of intellectualdisability (1,2).

The clinical manifestations are oftensubtle or not present at birth, due to trans-placental passage of somematernalthyroid hormone whilemany infants have somethyroid production of theirown (3).

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CH maybecaused by abnormaldevelopment or function of the thyroid gland, or of the hypothalamus and pituitary, but also to impaired TH action (4).

CH isclassifiedinto permanent and transientwhichrefers to a temporarydeficiency of thyroid hormone, discovered at birth, but thenrecovering to normal thyroid hormone production (3).

The immediate goals of treatment are to rapidlyraise the serum T4 and normalizeserum TSH levels, whilefrequentlaboratory monitoring in infancyis essential to ensure optimal neurocognitive outcome (3).

With the advent of screening of newborn populations, the incidence wasreported to be in the range of 1/3000 to 1/4000 (3).

Aims:-

Wewillpresent a case of congenitalhypothyroidism in a sibling of 3, in order to:

- Underline the importance of earlydetection of CH
- Explore the transient nature of congenitalhypothyroidism
- Investigate the genetic causes of primarycongenitalthyroiddysfunction
- Highlight the benefits of frequent initial follow-up

Case report :

Symptomatologyseems to date back to the age of 3 months in the first two siblings, for whichtheywerehospitalized in pediatrics for hypotoniawithmacroglossia. The check-up revealedhypothyroidismwith respective TSH at 400 ui/l and 100 ui/l for botheldersistersregardinglowperipheral hormone levels T4 and T3 (< 0.1 pmol/l) all evolving in a context of anemia.

Contrastingwith the youngest sibling whowasscreened at day 7 of life withlower TSH levels at 11 uui/l.

Cervical ultrasoundrevealed normal thyroid volume, while technetium-99 thyroidscintigraphyshowed a thyroid gland of normal size and moderatelyreduced fixation.

Acutelycomplicated for the 2nd sister by 2.3cm auricular septal defectwithpulmonary hypertension, and dilatation of the right cavities, with indication for urgent surgicalclosure. Successfullyoperated on one monthlater.

Unfortunately, the geneticanalysiswas not performedinitially, but iscurrentlyunderway.

Theywere all put on LT4 10 mcg/kg/d,with progressive adjustments.

However, the youngest sibling showedspontaneousimprovement, leading to cessation of hormone replacement therapy at the age of 5.

Discussion:-

Thyroid hormones, produced by the thyroid gland, are essential to the development, growth, and metabolism of practically all human tissues. TH production (T4 and T3) isregulated by the hypothalamic-pituitary-thyroid axis. A TH deficiency, at birth, or congenitalhypothyroidism (CH) results in severe retardation of growth and neuropsychomotordevelopment in the absence of replacement therapyinitiatedquicklyfrom the neonatalperiod (5).

Many of the classicfeatures (large tongue, hoarsecry, facial puffiness, umbilicalhernia, hypotonia, mottling, cold hands and feet and lethargy…), whenpresent, are subtle. In addition to the aforementionedfindings, nonspecificsignsthatsuggest the diagnosis of neonatalhypothyroidisminclude: prolonged, unconjugatedhyperbilirubinemia, gestation longer than 42 weeks, feedingdifficulties, delayed passage of stools, hypothermia, or respiratorydistress in an infant weighing over 2.5 kg (5).

To deal withtheseunexpressiveclinical vignettes,several guidelines and expert opinions on congenitalhypothyroidism (CH) are currentlyavailable,startingwithrequiring initial screening. On the samelevelalsocomes the need for fast,

effective treatment to ensureproper global functions, bettergrowth and, above all, optimal psycho-motordevelopment (6,7,8).

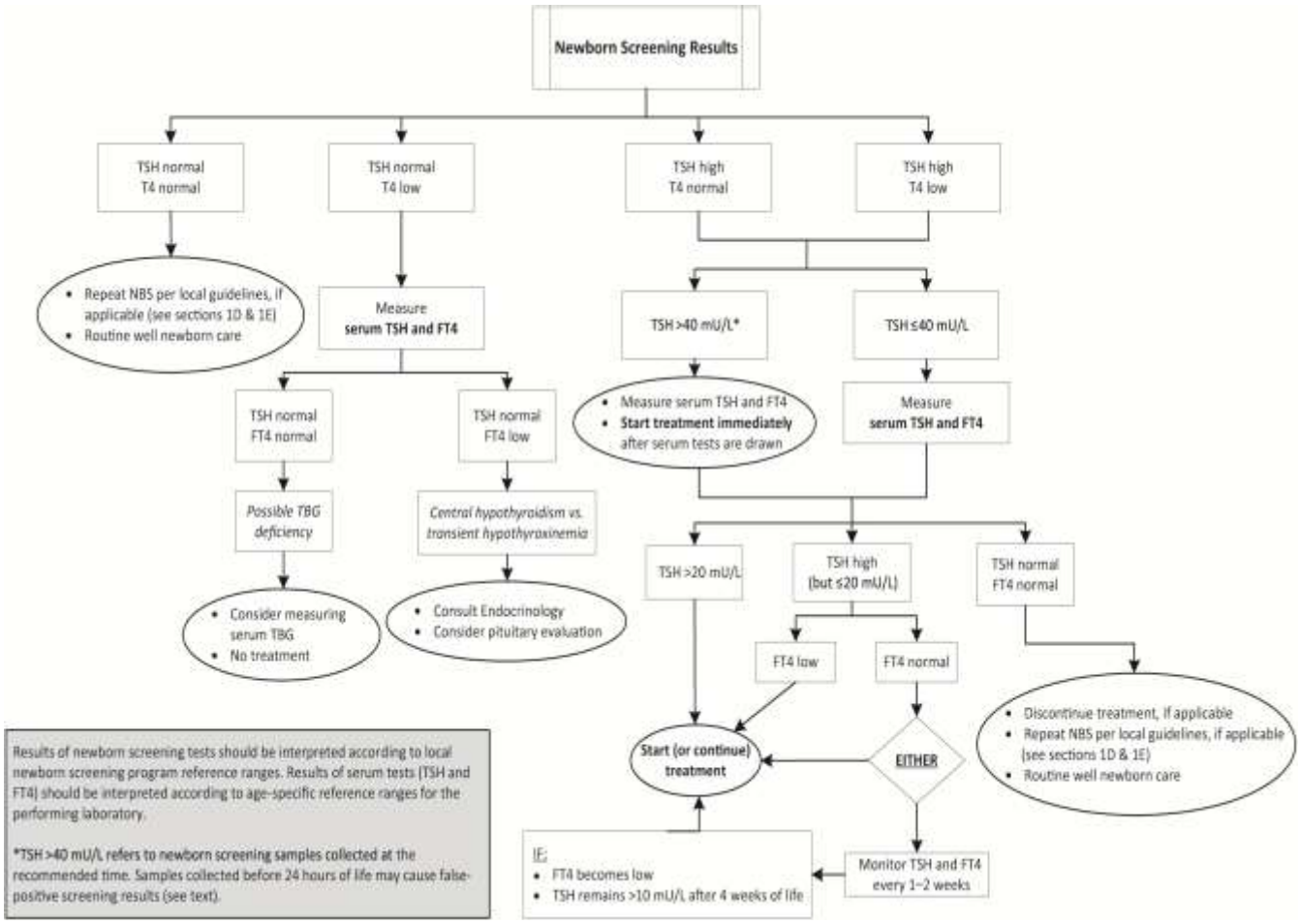


Figure N 1:- Screening recommandations (8).

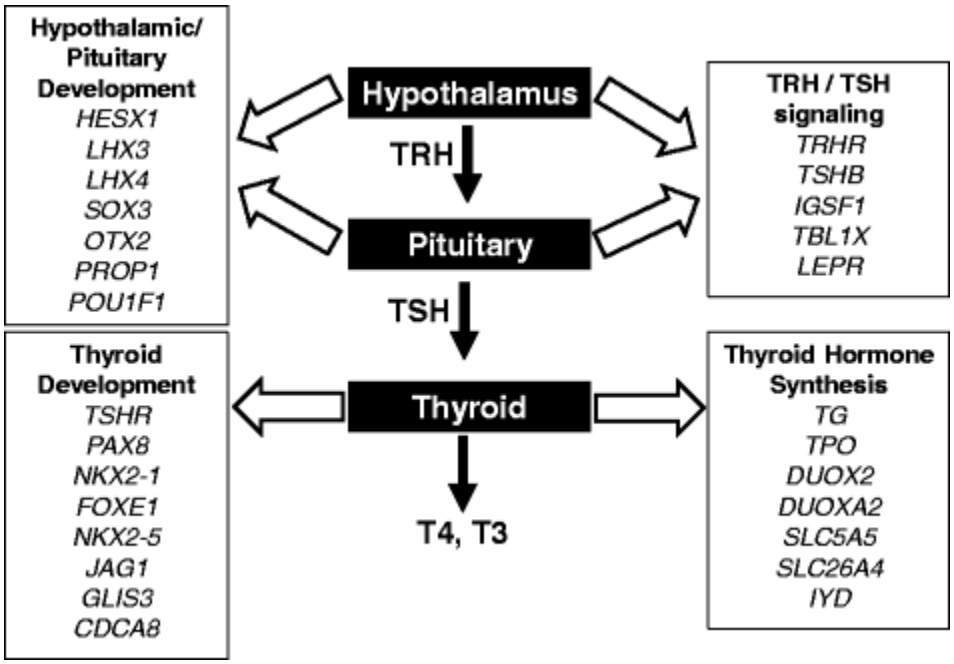
There isnow a well-establishedcorrelationbetween the occurrence of CH and the alteration of thyroiddevelopment. The Nkx2-1, Foxe1, Pax8, and HHex transcription factors are essential for the specification of the thyroid. Migration of the progenitorcellsis a crucial stage for development and thyroidfunction. The markers of terminal differentiation are the TSH receptor (TSHR), the iodine transporter (NIS, sodium/iodinesymportercoded by the SLC5A5 gene), thyroglobulin (TG), thyroperoxidase (TPO), DUOX2 and DUOXA2, involved in hormone synthesis . Iodine, drawnfrom the bloodstream, enters the thyrocytethrough the iodine transporter (NIS). The iodineisthenoxidized by TPO and the H_2O_2 DUOX2/DUOXA2 producercomplex to TG, TH matrix protein, T4, and T3. Malformations at any stage of thyroiddevelopment (such as the specification, proliferation, migration, growth, organization, differentiation, and survival) canresult in a congenitalabnormality and/or an alteration to hormone synthesisleading to varyingdegrees of hypothyroidism (2,7).

Whileransienthypothyroidismmaybecaused by neonatalfactorsincluding : neonataliodinedeficiency or excess, congenitalliverhemangiomas and mutations in the genesencoding for DUOX and DUOXA2, thatwe suspect in our sibling due to the transientcaracter in youngerbrother.

In fact if only one copy of the DUOX2 or THOX geneismutated, somehydrogenperoxideisproduced. As a result, thyroid hormone levels are slightlyreduced, causingmildcongenitalhypothyroidism. Sometimes, mildcongenitalhypothyroidismistemporary (transient), and thyroid hormone levelsthat are lowduringinfancyincreasewithage (9,10).

	Gene locus	Inheritance
Monogenicforms of thyroiddysgenesis		
Thyroidstimulating hormone receptor (TSHR)		AR
NK2 1 (NK2-1, TTF1) brain-lungthyroid syndrome	14q13	AD
Paired box gene 8 (PAX8)	2q11.2	AD
Forkhead boxE1 (FOXE1, TTF2) (Bambforth-Lazarus syndrome)	9q22	AR
NK2 homeobox 5 (NKX2-5)		
New candidate genes		
Nertrin 1 (NTN-1)		
JAG1	20p.12.2	
Glis3	9p24.2	AR
Inbornerrors of thyroidhormonogenesis		
Sodium/Iodidesymporter (SLC5A5, NIS)	19p13.2	AR
Thyroidperoxidase (TPO)	2p25	AR
Pendred syndrome (SLC26A4, PDS)	7q31	AR
Thyroglobulin (TG)	8q24	AR
Iodothyrosinedeiodinase (IYD, DEHAL1)	6q24-25	AR
Dual oxidase 2 (DUOX2)	15q15.3	AR/AD
Dual oxidase maturation factor 2 (DUOXA2)		AR/AD
CENTRAL HYPOTHYROIDISM		
Isolated TSH deficiency		
TRHR	14q31	AR
TSHB	1p13	AR
Isolated TSH deficiency or combinedpituitary hormone deficiency		
Immunoglobulinsuperfamily member1 (IGSF1) genedefects	Xq26.1	X-Linked
Combinedpituitary hormone deficiency		
POU1F1	3p11	AR, AD
PROP1	5q	AR
HESX1	3p21.2-21.2	AR/AD
LHX3	9q.34	AR
LHX4	1q25	AD
SOX3		X-linked
OTX2		AD

Figure N 2:-Genetic causes of CH (5).



Figune N3:-Gene causingcongenitalhypothyroidism.

Levothyroxine (l-thyroxine) is the treatment of choice, and American academy of pediatrics and European society of pediatricendocrinologyrecommend 10-15µgm/kg/day as initial dose. The immediate goal of therapyis to normalize T4 within 2 weeks and TSH within one month. The overall goal of treatmentis to ensuregrowth and neurodevelopmentaloutcomes as close as possible to theirgeneticpotential(2). And thiswasindeed the case of the 2nd sibling, a levothyroxinetreatmentwasstartedduring the first weeks of life, whichallowed good psychomotordevelopment and growth.

Conclusion:-

New born screening and effective treatment for congenitalhypothyroidism has been included in neonatal programmes and isconsidered as a major achievement in preventivemedicine. But still more efforts required to raiseawareness of this importance in developing countries

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