LOWERING OF THE TSH CUT-OFF LIMIT SUBSTANTIALLY ALTERS UNIVERSALLY ACCEPTED KEY FEATURES OF CONGENITAL HYPOTHYROIDISM.
RECONSIDERATION OF THE USE OF FT4 LEVELS FOR DIAGNOSIS AND TREATMENT

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Background knowledge

The term **Congenital Hypothyroidism (CH)** describes children with subnormal thyroid hormone levels present at birth. According to literature, CH has an incidence of **~1:1500-1:3000 births** with a clear predominance of females (**female:male ratio 2:1**) and is mainly caused by **thyroid dysgenesis (80%).** Although not currently a proposed factor (ESPE Guidelines for CH, 2014), low FT4 levels (<8 pg/mL) have been used as an important criterion for CH diagnosis and treatment initiation.

The **National Greek Neonatal CH screening program** was initiated in 1980 and is carried out by a **single laboratory** that receives and tests the Guthrie cards from all the maternity hospitals in Greece. Over the last 35 years, more than **3,690,000 neonates** have been screened. The program has followed the TSH cut-off limit lowering-trend, observed worldwide, from the initial 35 to 6 mIU/L. TSH levels above the cut-off limit is not the diagnostic criterion for CH but initiates monitoring and follow-up.

Objective and hypotheses

To assess the impact of the TSH cut-off limit decrease on key CH features, such as incidence, gender differences (i.e., female to male ratio), cause (dysgenesis) and FT4 levels as a diagnostic criterion.

Patients and Methods

Data from the medical records of children diagnosed with CH through the Greek Neonatal CH screening program were reviewed (**n=2445**). Patients were diagnosed during the last 35 years using variable TSH cut off limits ranging from 30 to 6 mIU/L.

Results

CH incidence has progressively increased from 1980 to 2014 following the decrease of the TSH screening cut-off limits (**Figure 1**). Data from all the calendar years that share the same TSH cut-off limit (i.e., 6, 8, 10, 15, 30 and 35 mIU/L) were grouped together. As expected, an increase in CH incidence is observed when moving from a cut-off limit of 35 to 6mIU/L (from 1:3500 to 1:435 respectively, **Figure 2**) .

Female to Male Ratio: Using the TSH cut-off limit of 35mU/L, females comprised 70% of CH patients whereas, using a cut-off limit of 10mIU/L or below (i.e., last 15 years for Greece) marginal male preponderance is observed (**Figure 3**).

CH etiology: In a total of 1839 patients in whom ultrasonographic data were available, thyroid dysgenesis was observed in only 16%. A progressive decrease in the incidence of dysgenesis among CH patients is evident when moving from the cut-off limit of 30 mIU/L to 6 mIU/L (from 73% to 10,5%, **Figure 4**).

CH and euthyroidism at diagnosis (FT4 levels >8,5 pg/mL): A progressive increase in the incidence of euthyroidism at diagnosis among CH patients is evident when moving from the cut-off limit of 35 mIU/L to 6 mIU/L (from 14 to 90%, respectively, **Figure 5**). **Normal FT4 levels at diagnosis** were observed in 30% of patients with thyroid dysgenesis, 11.5% of patients with initial TSH >80 mIU/L and 67% of patients receiving a relatively high LT4 dose (>3 μg/kg/d) at the age of three years and had thyroid in situ (**Table 1**).

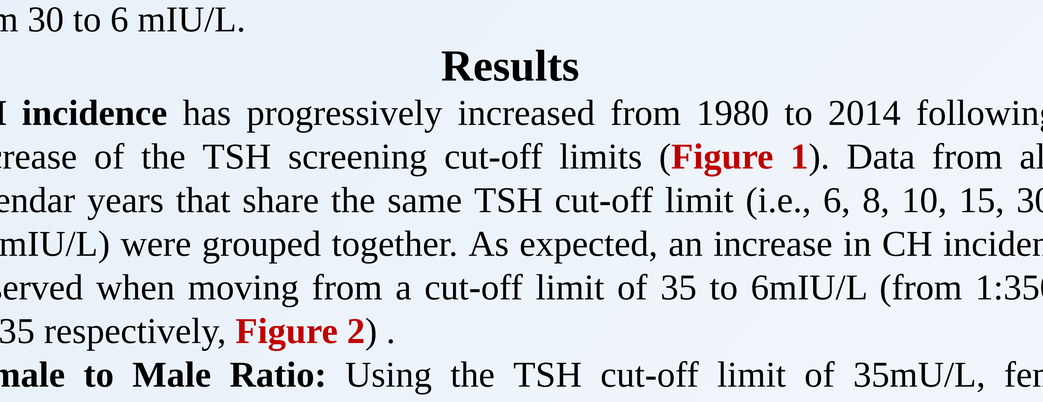
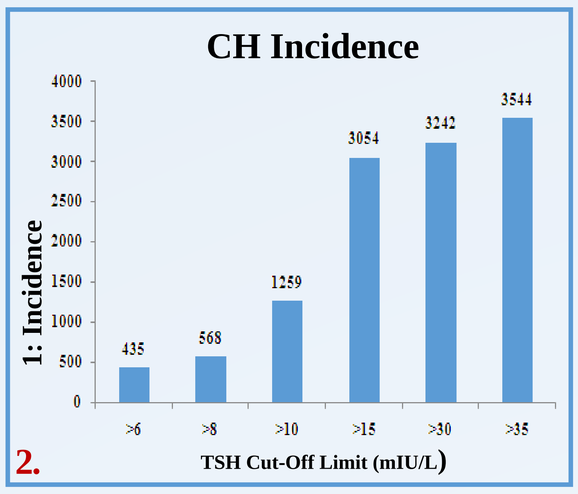


Figure 1: CH incidence from 1980 until 2014 is depicted (data from the Greek CH screening program including >**3,690,000** neonates). The corresponding TSH cut-off limits are depicted on top. A progressive increase in CH incidence is observed within the last 35 years following the lowering of cut-off limits.



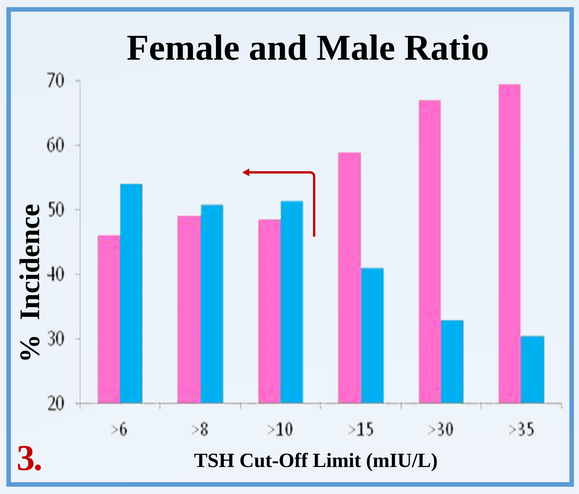
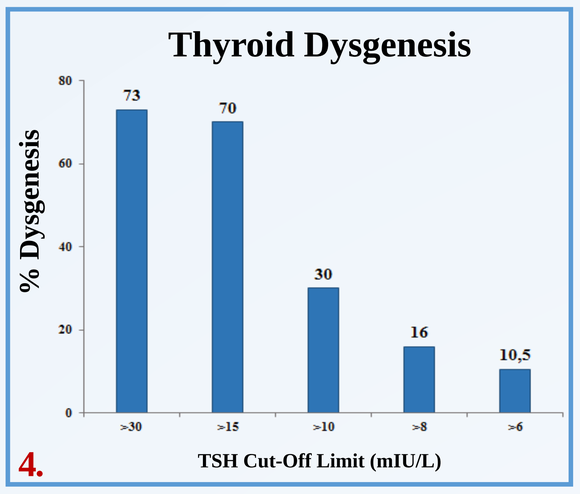


Figure 2: CH incidence with respect to TSH cut-off limit used (data from 1980 until 2014, Greek CH screening program). A progressive decrease of CH incidence is evident when moving from a cut-off limit of 6 mIU/L (1:435) to 35 mIU/L (1:3544) .

Figure 3: Percent of **female** and **male** neonates diagnosed with CH (data from 1980 until 2014, Greek CH screening program). Marginal male preponderance is observed when a cut-off limit of 10 mIU/L or below is applied (red arrow). **The impact of the TSH threshold limit on CH incidence and female to male ratio is apparent.**



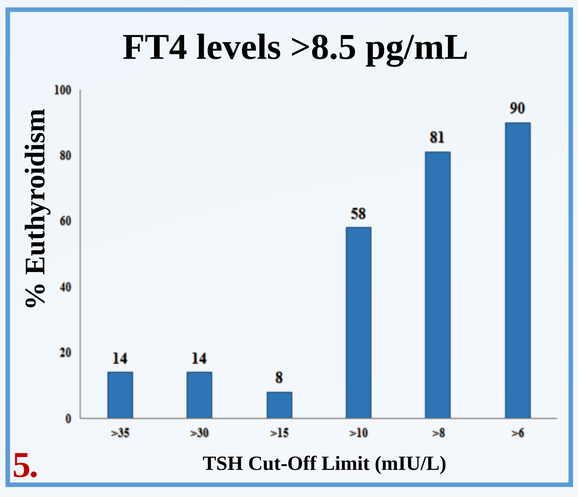


Figure 4: Percent of thyroid dysgenesis among CH patients with respect to the TSH cut off limit applied. A progressive decrease in the incidence of dysgenesis is evident when moving from the cut-off limit of 30 mIU/L to 6 mIU/L. **The impact of the TSH threshold limit on CH etiology is evident: thyroid dysgenesis is not the major cause of CH.**

Figure 5. Percent of patients with FT4 levels >8,5 pg/mL (i.e., euthyroidism) among CH patients at diagnosis with respect to the TSH cut-off limit. A progressive increase in the incidence of euthyroidism at diagnosis when moving from the 35 mIU/L to 6 mIU/L cut-off limit is evident.

Group (n)		FT4 >8,5 pg/mL at diagnosis
Dysgenesis	(n=307)	**30 %**
Initial TSH >80 mIU/L	(n=369)	**11,5 %**
LT4 dose >3 μg/kg/d at age 3 years	(n=130)	**67 %**

Table 1: Percent of euthyroidism (FT4 levels >8,5 pg/mL) at diagnosis among patients with dysgenesis, initial TSH >80 mIU/L and relatively high LT4 dose at the age of 3 years (thyroid in situ).

Conclusions

1) Lowering of the TSH cut-off limit substantially affects the universally accepted key CH features: incidence is higher, male predominance is observed and thyroid dysgenesis is not the main etiology of CH.

2) Screening programs lead to early CH diagnosis when FT4 levels may still be normal even in severe CH cases. Therefore, our **data strongly support current ESPE guidelines** that normal FT4 values should not affect our decisions for CH diagnosis and LT4 therapy initiation. In accordance, the term "hypothyroidism" does not adequately describe the spectrum of disorders of thyroid function observed during the neonatal period and may need to be modified.

Acknowledgments

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