Letter to the Editor

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Rational approach to the primary evaluation of thyroid disease in paediatrics. Full thyroid profile vs. thyroid-stimulating hormone and free thyroxine only

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To the Editor,

Healthcare budgets worldwide are facing increasing pressure to reduce costs and improve efficiency, while maintaining quality. Laboratory testing has not escaped this pressure.

The clinical laboratory control of demand is often confused with demand management. Control of demand refers to the reduction of costs, while demand management focusses on ensuring appropriate requesting. Hence, the latter has an inbuilt quality aspect and may result in increased as well as decreased testing (i.e. to reduce overordering, underordering and misordering of tests) [1, 2].

It has been widely accepted that the major changes in thyroid function in adult subjects may initially be studied by assessing of thyroid-stimulating hormone (TSH) [3]. Free thyroxine (fT4) should be measured in the setting of an abnormal TSH, and free triiodothyronine (fT3) only in specific circumstances, such as cases of suspected hyperthyroidism with a normal fT4 and suppressed TSH [4].

The recommendations by Wisely et al. [5] from the American Society for Clinical Pathology (ASCP) advise against ordering multiple tests in the initial investigation of patients with suspected non-neoplastic thyroid disease.

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In the paediatric population the impact of thyroid hormone deficiency on neuro development and growth, warrant evaluation of an aetiology of central origin. Here we propose the use of serum TSH and fT4 to evaluate primary and central thyroid dysfunction in this population [6, 7]. However, to our knowledge, currently no evidence exists on whether serum TSH and fT4 provide sufficient information for the screening of thyroid function in children.

The aim of the study was to retrospectively assess serum full thyroid profile (TSH, fT4, T4 and T3) vs. TSH and fT4 only for the primary evaluation of thyroid disease in children describing the results obtained and subsequent medical management.

We retrospectively analysed consecutive patients (n = 5999) in whom thyroid function was studied with a full thyroid test seen between November 2014 and September 2015. Tests were performed on the day of sampling. We excluded those subjects who were previously diagnosed with thyroid disease, those that were not seen by any physician after the studies, those who had been treated with levothyroxine (LT), methimazole, or antiepileptic drugs, and severely ill patients. The remaining 5738 subjects included were categorised into 12 groups according to age from 1 week to 12 years. TSH, T3 and fT4 were measured with Architect i4000 (Abbott) and we used our own reference interval (RI) [8] for total T4 IMMULITE 2000 (Siemens) and was used the RI by Elmlinger et al. [9]. All with percentiles between 2.5 and 97.5.

Subjects with serum TSH and fT4 within the (RI) according to age were selected (n = 4007, 69.8%). From this group, children who had T3 and/or T4 outside the RI were selected (n = 390, 6.79%) (Figure 1) (Supplementary Material 1 and 2).

In the clinical records (CR) of 381 patients (6.63%) no comment was made on thyroid function or the thyroid profile was reported to be normal, in spite of T3 and/or T4 outside the RI.

In nine patients (0.15%) a comment was made in the CR; five patients were sent home without further

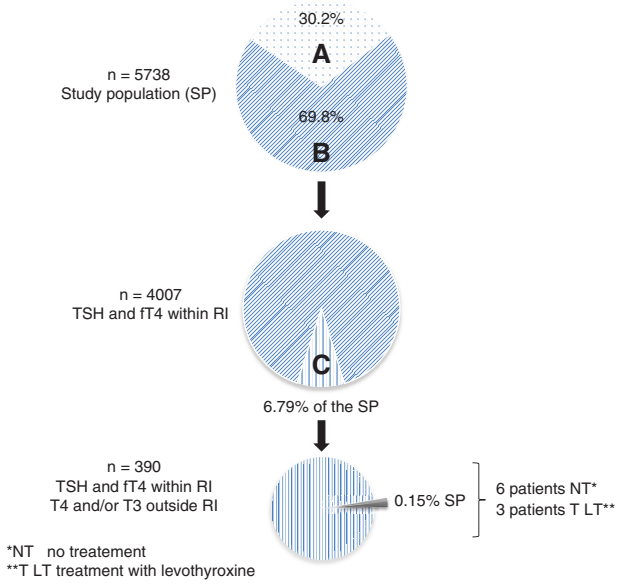

Figure 1: Selection sequence of patients in whom thyroid function was studied.
(A) Patient with TSH and/or fT4 outside the RI. (B) Patients with TSH and fT4 within the RI and (C) Patients with TSH and fT4 within RI and T3 and/or T4 outside RI. Three patients T LT: 0.05%, six patients NT 0.10%.

interventions, in one patient with high T3 and T4, high serum levels of thyroxine-binding globulin were found, and the three remaining were finally treated with LT (0.05% from de selected subjects). All of them had fT4 below the 10th percentile of the RI and one additionally had TSH above the 90th percentile of the RI.

Of the study population n = 5738, 69.8% presented with normal serum TSH and fT4 levels. Overall patients, 6.79% had T3 and/or T4 outside the RI, which is statistically acceptable for a reference population. According to the definition of RI using the central 95% values from reference population in both analytes, 5% of healthy subjects is statistically expected to be found outside the RI, if we used two analytes is possible to found almost 9.75% of healthy subjects outside the RI ($[1–(0.95)^2] * 100 = 9.75\%$).

In the CR of 381 patients (6.63%) no comment was made, this may have happened because in all cases T3 and/or T4 were within the reference change value (RCV) on the limits of the RI (Supplementary Material 2).

As to the nine patients that had some medical comment in their CR regarding thyroid test results, only three were put on treatment, and all had fT4 below the 10th percentile and one had TSH above the 90th percentile as well. Moreover, the three patients who during follow-up showed a drop in serum thyroid hormones, and showed clinical signs of hypothyroidism and were started on supplementary treatment with LT had medulloblastoma, neurofibromatosis and Prader-Willi syndrome, diseases that may be associated with central hypothyroidism (Table 1).

Table 1: Clinical and laboratory feactures of patients in whom some comment on the results of T3 and/or T4 was made in the clinical records.

Patient (sex)	Age, years	TSH	fT4	T4	T3	Diagnosis	1-year follow-up (TSH/fT4/T4/T3)	Treatment
1 (M)	3	1.08	1.4	16.4	3.63	Short stature	High TGB (53.8, µg/mL) (1.34/1.12/17.0/3.52)	NT
2 (M)	9	1.71	0.89	5.2	1.28	Short stature	No changes (1.85/0.89/5.7/1.11)	NT
3 (F)	2	1.88	1.11	10.1	2.36	Unknown	No changes (1.31/1.09/9.2/2.08)	NT
4 (F)	1	2.45	1.12	4.8	2.02	Unknown	No changes (2.33/1.06/6.5/1.41)	NT
5 (F)	12	1.89	0.88	4.9	1.44	Developmental delay	Low T4 was recorded (2.74/0.82/5.1/1.31)	NT
6 (M)	11	2.99	1.23	10.2	2.06	Developmental delay	High T3 was recorded (2.72/1.26/8.9/1.98)	NT
7 (M)	8	4.55[a]	0.99[b]	6.3	1.78	Medulloblastoma	Dropped fT4,T4 and T3 (4.58/0.90/6.0/1.53)	T LT
8 (M)	10	2.05	0.86[b]	5.1	1.44	Prader-Willi syndrome	Dropped fT4 and T4 (0.73/0.83/4.9/1.27)	T LT
9 (M)	10	1.44	0.98[b]	6.1	1.32	Neurofibromatosis	Dropped T4 and T3 (1.33/0.98/6.0/0.83)	T LT

M, male; F, female; NT, no treatement; T LT, treatment with levothyroxine. [a]Over 90th percentile. [b]Below 10th percentile. Units: TSH – µIU/mL, fT4 – ng/dL, T4 – µg/dL, T3 – ng/mL. To convert thyroid hormone values to metric units use the following factors: T3 – nmol/L = 1.538*T3 – ng/mL; T4 – nmol/L = 12.87*T4 – µg/dL and fT4 – pmol/L = 12.87*fT4 – ng/dL.

In adults the use of only serum TSH by primary care providers, may be sufficient for screening of thyroid disease. However, in children functional disorders of the thyroid, such as hypothyroidism and hyperthyroidism due to chronic lymphocytic thyroiditis and Graves' Basedow disease, are frequent. The combination of TSH and fT4 allows detection of these two disorders as well as the central abnormalities of the hypothalamus pituitary thyroid axis; the findings in our series support this concept.

When considering cost-effectiveness, costs could be reduced by 46% in each patient studied, with a positive impact on the management of demand without effecting clinical outcome.

In conclusion, we found that the use of TSH and fT4 is useful for primary evaluation of thyroid disease in paediatrics. However, TSH and fT4 should be assessed with a stricter RI between the 10th and 90th percentile. In case of persistent clinical signs suggestive of a disorder of the thyroid gland in a child, assessment of a complete thyroid profile, including antithyroid antibodies, total or free T3, and total T4, is recommended.

This study suggests that questionable testing patterns contribute to inappropriate thyroid test utilisation. A prospective study in a paediatric population would be necessary to clinically confirm these results and subsequently define medical management.

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