

Patterns of serum thyroglobulin in infants referred with high TSH on newborn screening compared with iodine-sufficient healthy controls

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Introduction - Aim

- Thyroglobulin (Tg) is exclusively synthesised by thyroid tissue and is potentially useful in diagnosis of the etiology of congenital hypothyroidism (CH). However, its role has yet to be fully evaluated.
- The aim of the study was to examine the usefulness of Tg in helping define the etiology of CH.

Methods

- Tg samples from patients referred with TSH elevation on the Scottish screening program from January 2004-June 2018, and in 22 healthy iodine-sufficient babies from Czech Republic (2008-2012), were measured in a single laboratory, Glasgow Royal Infirmary, UK, by Immulite 2000 chemiluminescent immunometric assay (CVs 9.8, 5.7 and 5.7% at 1.6, 8.5 and 55 µg/l).
- Lower limit of detection was 2 µg/l.

Results

- Figure 1 shows that between 2004 and 2018, 395 infants were referred with capillary TSH elevation. Tg was sampled in 197 patients (49,9%) and samples were sufficient for analysis in 190 (120 female). Measurement was usually on days 10-12 for patients and day 3 for controls.

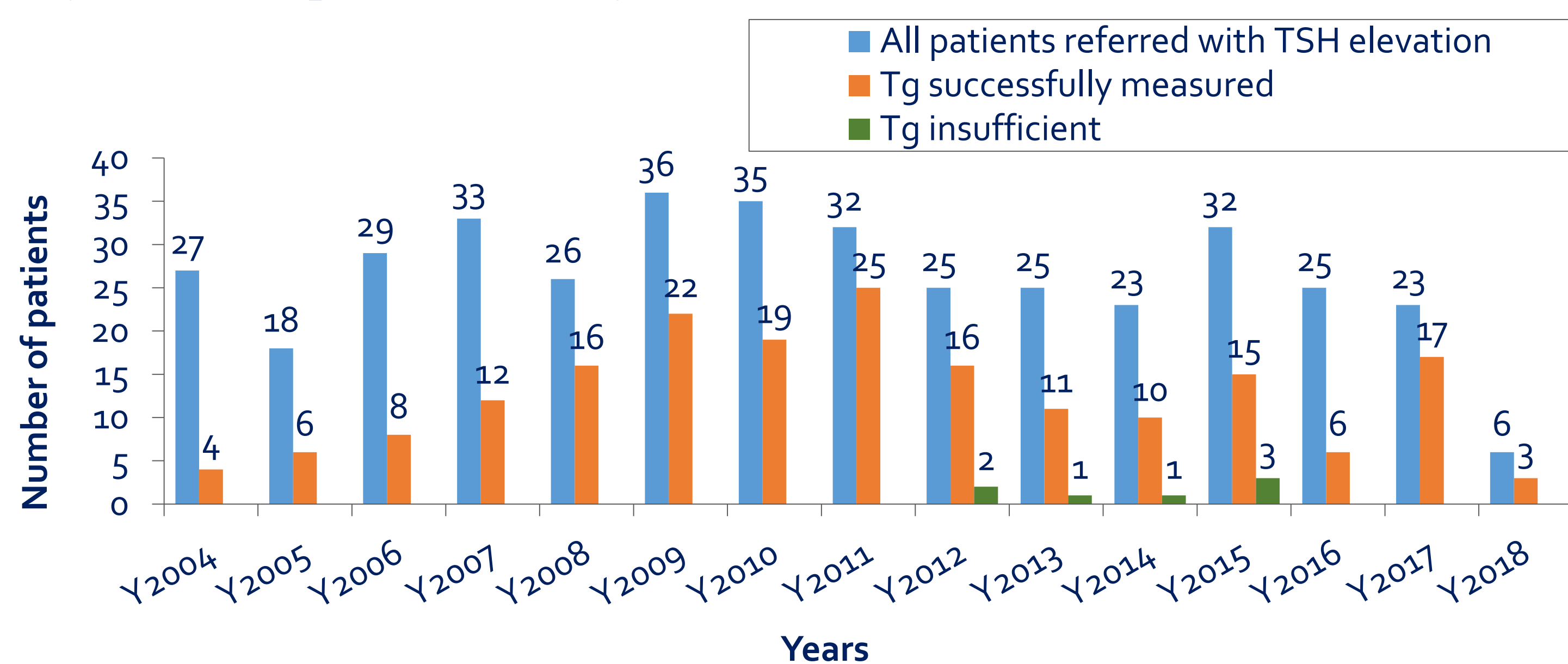


Figure 1. Number of patients that have had thyroglobulin measured between 2004-2018

- The category of TSH elevation (definite CH, probable CH, status uncertain and transient TSH elevation); and the cause of definite CH in the 190 children is shown in figure 2.

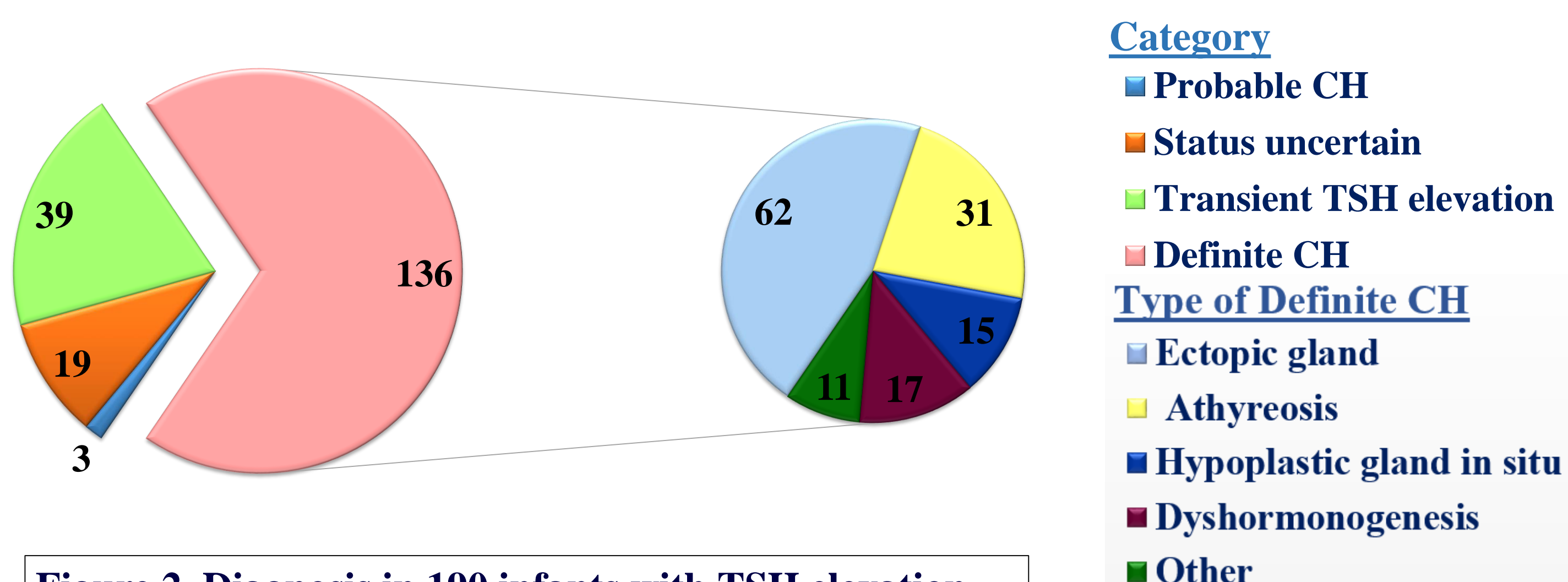


Figure 2. Diagnosis in 190 infants with TSH elevation

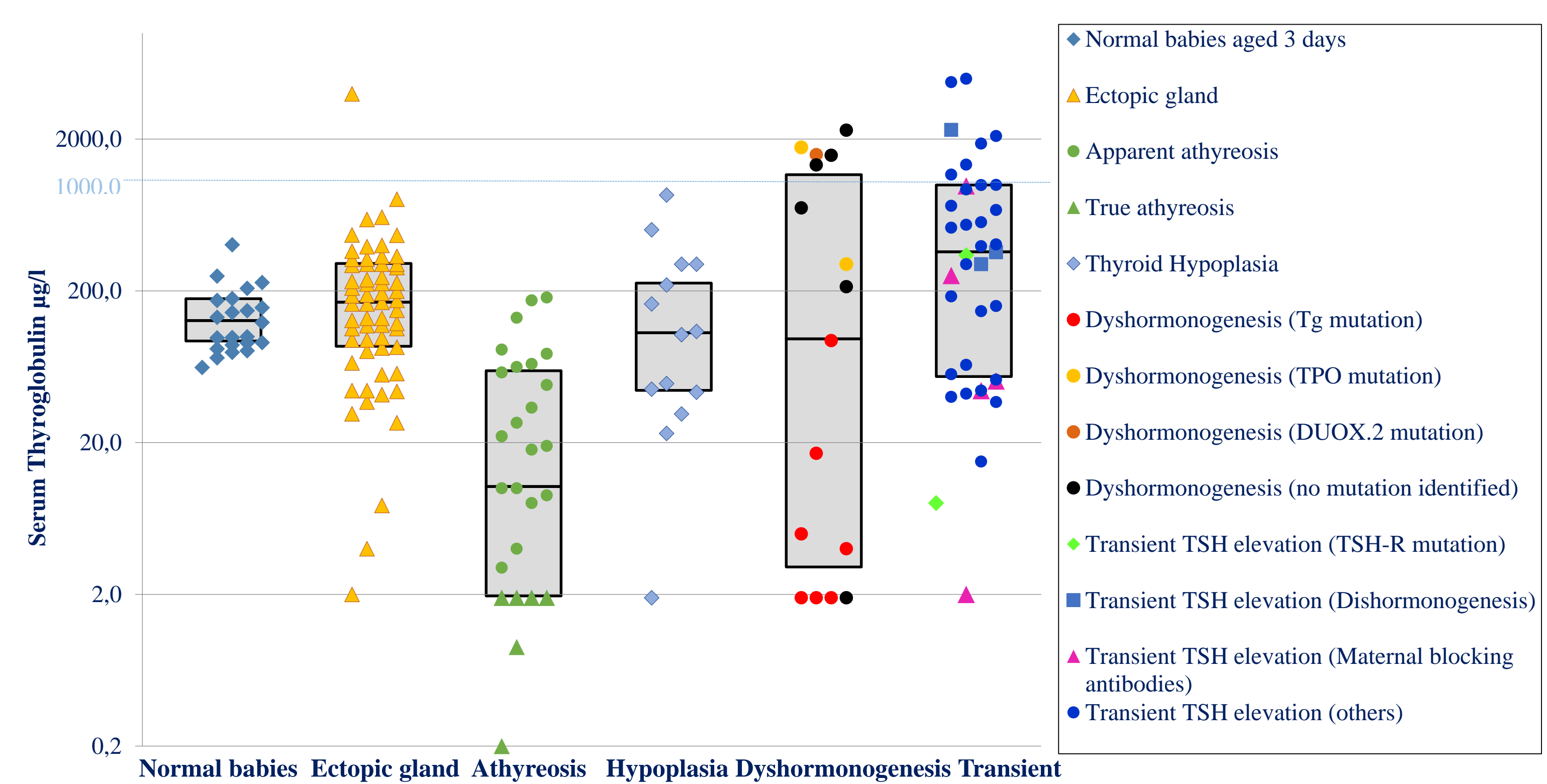
- The group of athyreosis was subdivided into apparent athyreosis (Tg recordable, n=20) and true athyreosis (Tg unrecordable, n=10).
- Causes of dyshormonogenesis in our patients were TPO defect (n=2), Tg defect (n=7), DUOX.2 mutation (n=1), and no mutation established (n=7).
- Transient hypothyroidism in our patients was related to dyshormonogenesis (n=3), TSH receptor mutation (n=2), maternal blocking antibodies (n=5) and cause unknown/other causes (n=29).

- The results of serum thyroglobulin levels in normal Czech infants, and patients with ectopia, athyreosis, hypoplasia, dyshormonogenesis, and transient CH are shown in table 1 and figure 3. p* = p values for differences between controls and CH groups according to cause.

Table 1. Serum thyroglobulin in patients with congenital hypothyroidism compared with normal Czech infants.

	N	Serum Tg level (µg/l)				p*
		Mean	SD	Median	Range	
Controls	22	140.4	78.8	111.90	62.5-403	
Cause of CH						
Ectopic gland	62	262.7	509.3	168	2-3977	0.180
Athyreosis	31	35.4	50.2	10	0.2-181	<0.001
Tg < 2µg/l	10	1.6	0.6	1.9	0.2-1.9	<0.001
Tg > 2 µg/l	20	52.3	54.2	30.5	3-181	<0.001
Thyroid Hypoplasia	15	196.35	237.73	105.5	1.9-857	0.721
Dyshormonogenesis	17	617.9	801.2	153.5	1.9-2287	0.906
Transient	39	757.7	1146.9	351.5	2-4995	0.101

- Figure 3. The distribution of Tg values in healthy iodine-sufficient Czech newborns, and patients with ectopia, athyreosis, hypoplasia, dyshormonogenesis, and transient CH, with median and interquartile ranges shown for each group.



- Tg was significantly lower in the athyreosis and DHG due to Tg mutation groups compared with controls (p<0.001).
- Tg was often higher (>1000 µg/L) in patients with dyshormonogenesis (n=6/19) compared with controls (p<0.001).
- However, there was considerable overlap between the control and patient groups.

Correlation between serum Tg and initial TSH values

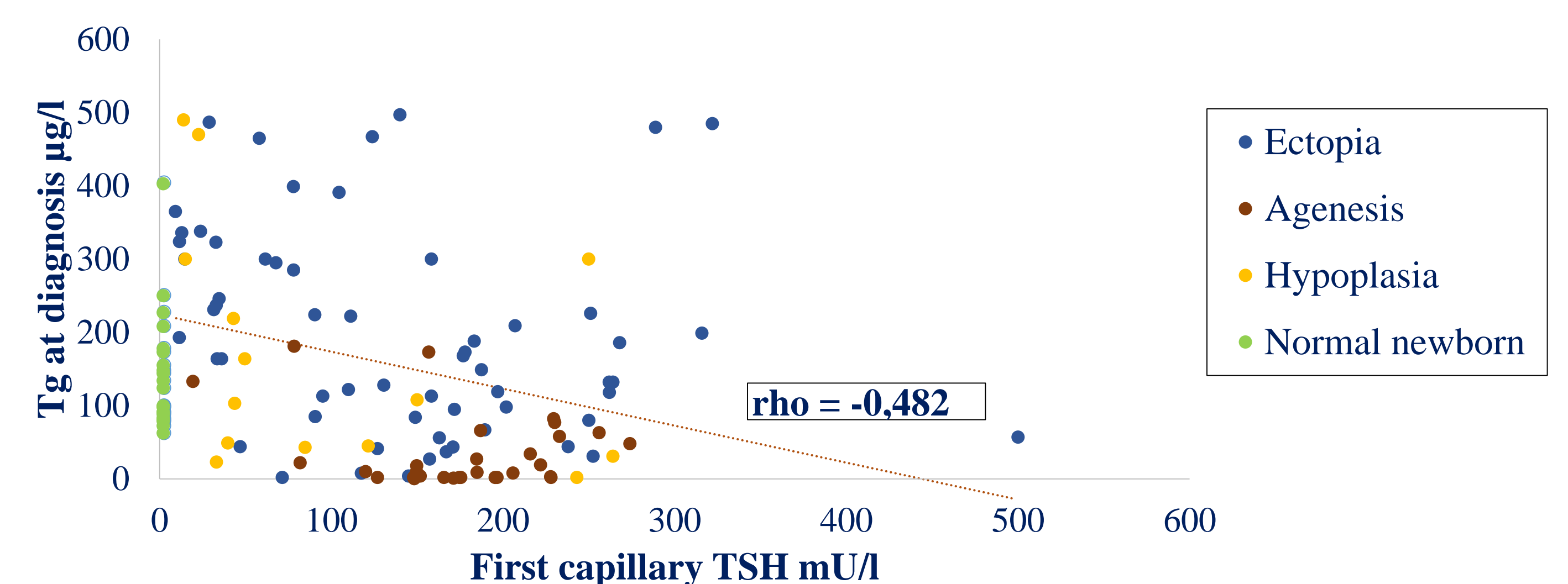


Figure 4. Correlation between TSH and Thyroglobulin

- There is a negative correlation between first capillary/venous TSH and serum Tg in normal newborns, and infants with ectopia, athyreosis and hypoplasia (figures 4). This indicates that TSH is higher in subjects with lower Tg and, presumably, less thyroid tissue.

Summary and conclusions

- Serum thyroglobulin is unrecordable in true athyreosis, very low in dyshormonogenesis due to Tg mutation, low in apparent athyreosis, variable but usually high (reflecting TSH drive) in thyroid ectopia, and often high in other forms of dyshormonogenesis.
- Thyroglobulin is of limited diagnostic value in CH in isolation unless it is very high (suggestive of some forms of dyshormonogenesis) or low (as seen in athyreosis and dyshormonogenesis due to Tg defect).
- However, Tg can be a useful adjunct to diagnosis in CH when interpreted together with thyroid function and imaging.
- The Tg level at birth in infants with CH is influenced by two factors: the amount of functioning thyroid tissue and the TSH drive caused by the hypothyroidism. Further work is required to show if initial Tg could be helpful in predicting levo-thyroxine (L-T4) requirement later in infancy.