

DIAGNOSIS OF CENTRAL CONGENITAL HYPOTHYROIDISM AND MULTIPLE PITUITARY DEFICIENCIES THROUGH A NEONATAL SCREENING PROGRAM

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The congenital central hypothyroidism (CCH) incidence is estimated at 1:18,000-30,000 neonates and most are included in multiple pituitary deficiencies (MPD)¹. Clinical depend on the etiology, the deficit severity; other associated hormonal alterations and the age of diagnosis². Neonatal screening (NS) for congenital hypothyroidism that includes T4 facilitate its diagnosis.

Objetives:

- To evaluate the characteristics of patients with CCH in the Basque Country.
- To evaluate the success of total T4 [TT4] in our neonatal screening (NS) for the early diagnosis of MPD.

Material and methods:

Retrospective study of 20 CCH controlled by pediatric endocrinologists of the Basque Country in the last 21 years [1997-2009: 426,174 live newborns]. The results of the NS performed at 48 hours of life, including [TT4] and TSH on filter paper³, as well as clinical, hormonal and image data have been collected. The lower cut-off point for [TT4] in NS is 6 µg/dL. Two cases without T4 levels were excluded.

The patients were classified according to [TT4] in 3 subgroups: <6 µg/dL (n=4), 6-8 µg/dL (n=8) and >8 µg/dL (n=6).

MPD was diagnosed with affectation ≥2 hormonal axes.

Adrenal insufficiency (AI) detected in the first year of life was considered determinant of severity.

The CCH incidence: 1/22,308 live newborns

Mean gestational age : 39 weeks (33-41)
Mean birth weight: 3,175 gr (2,300-4,100)
61% males

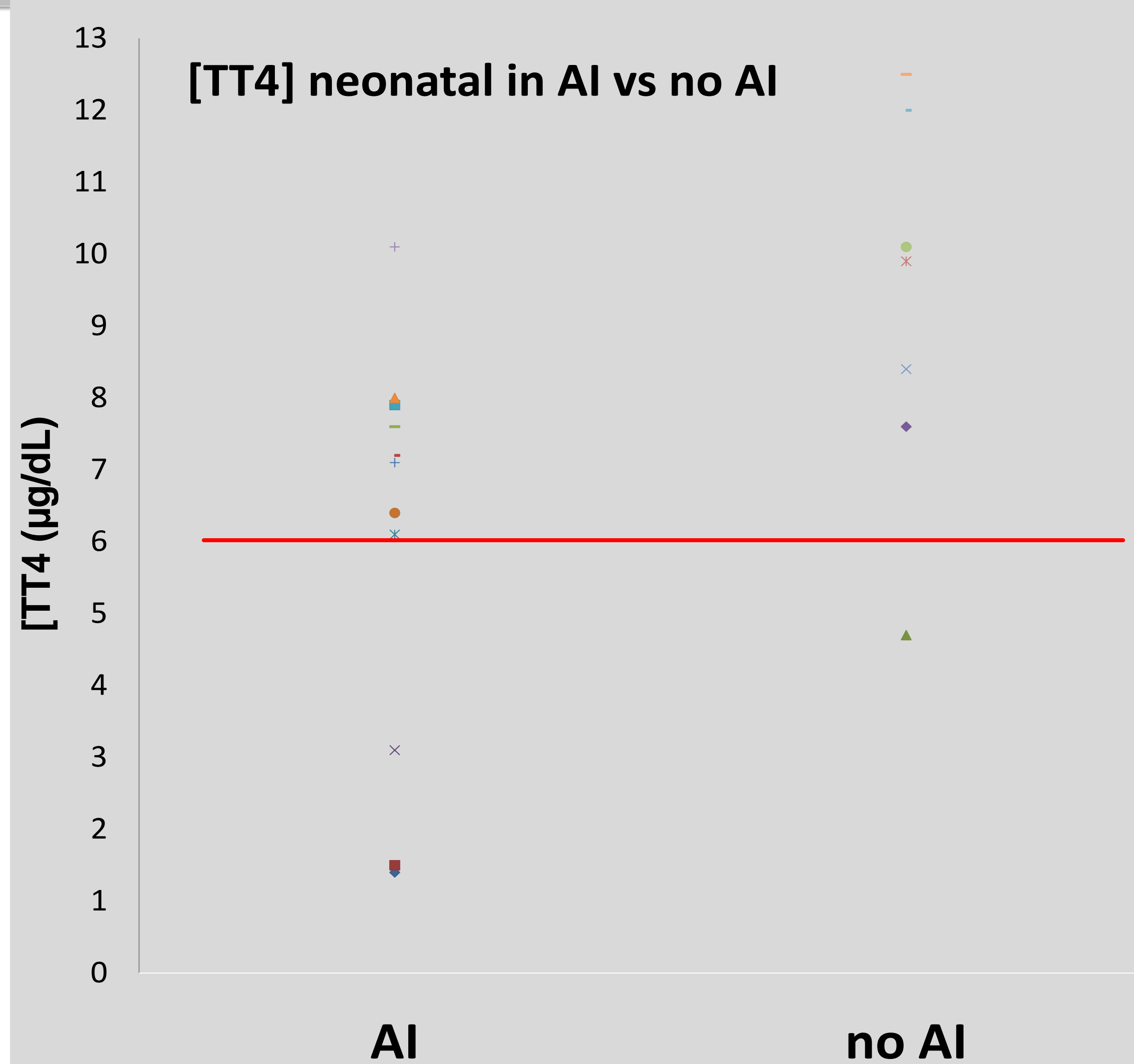
All patients had pituitary malformation and MPD

Magnetic Resonance Imaging

- 15 Pituitary stalk interruption syndrome (PSIS) variants: thin or interrupted pituitary stalk, aplasia or hypoplasia of the anterior pituitary (HAP) and absent or ectopic posterior pituitary (EPP)
- 3 Septal Optic Dysplasia (SOD)

Hormonal deficiency

- Growth Hormone Deficiency (GHD): 77%
- Adrenal insufficiency (AI): 61%
- Hypogonadism : 50% (13 patients considered)
- Diabetes Insipid: 11%



11/18 patients had AI and their average [TT4] in NS was lower

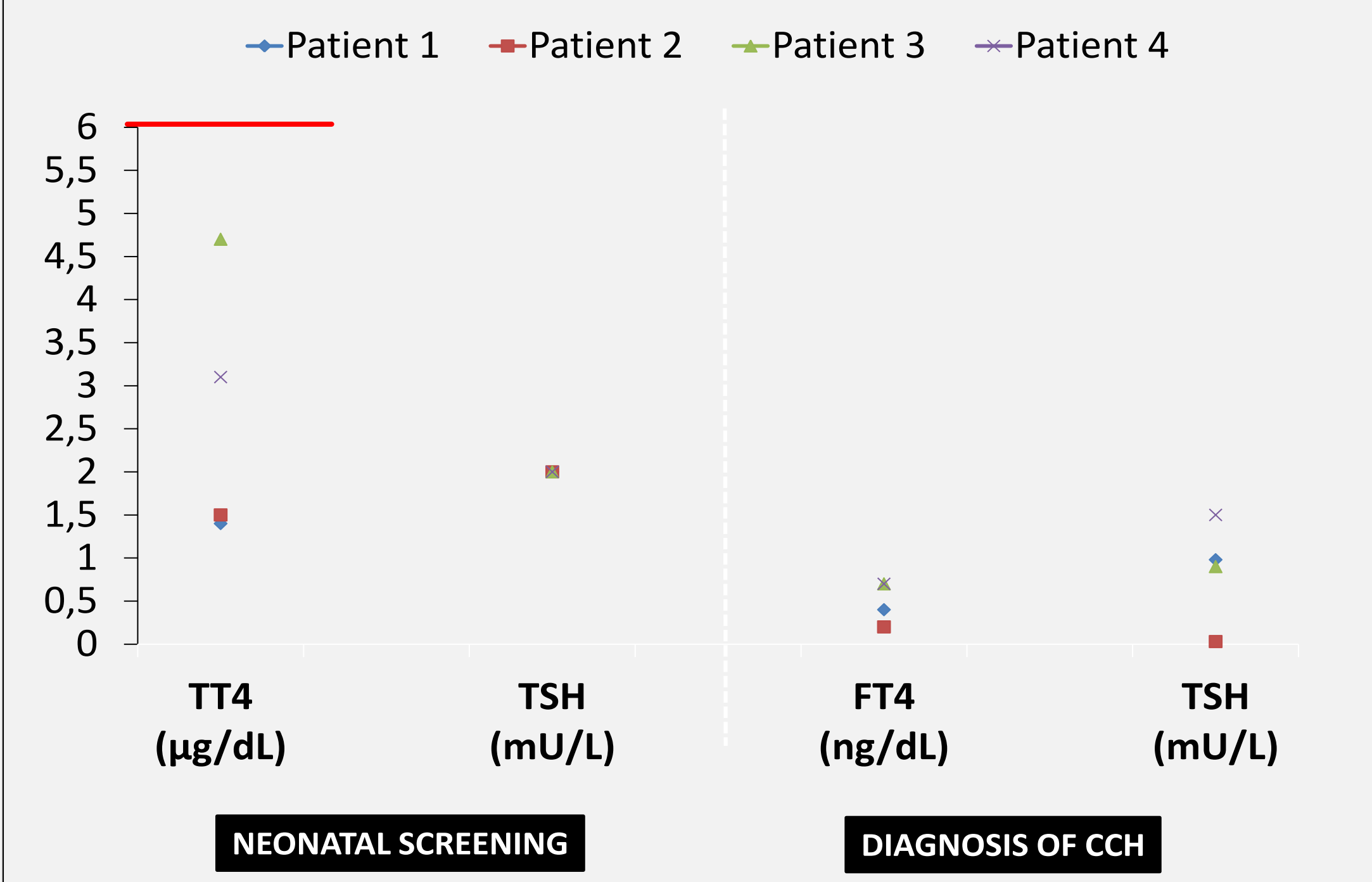
AI: 6±2.8 µg/dL vs non-AI: 8.9±3.5 µg/dL (U-Mann-Whitney p=0.03)

➤ **4 patients had [TT4] <6 µg/dL in NS**
Three of them were diagnosed of AI in the first month of life but the fourth maintains adrenal function at 5 years

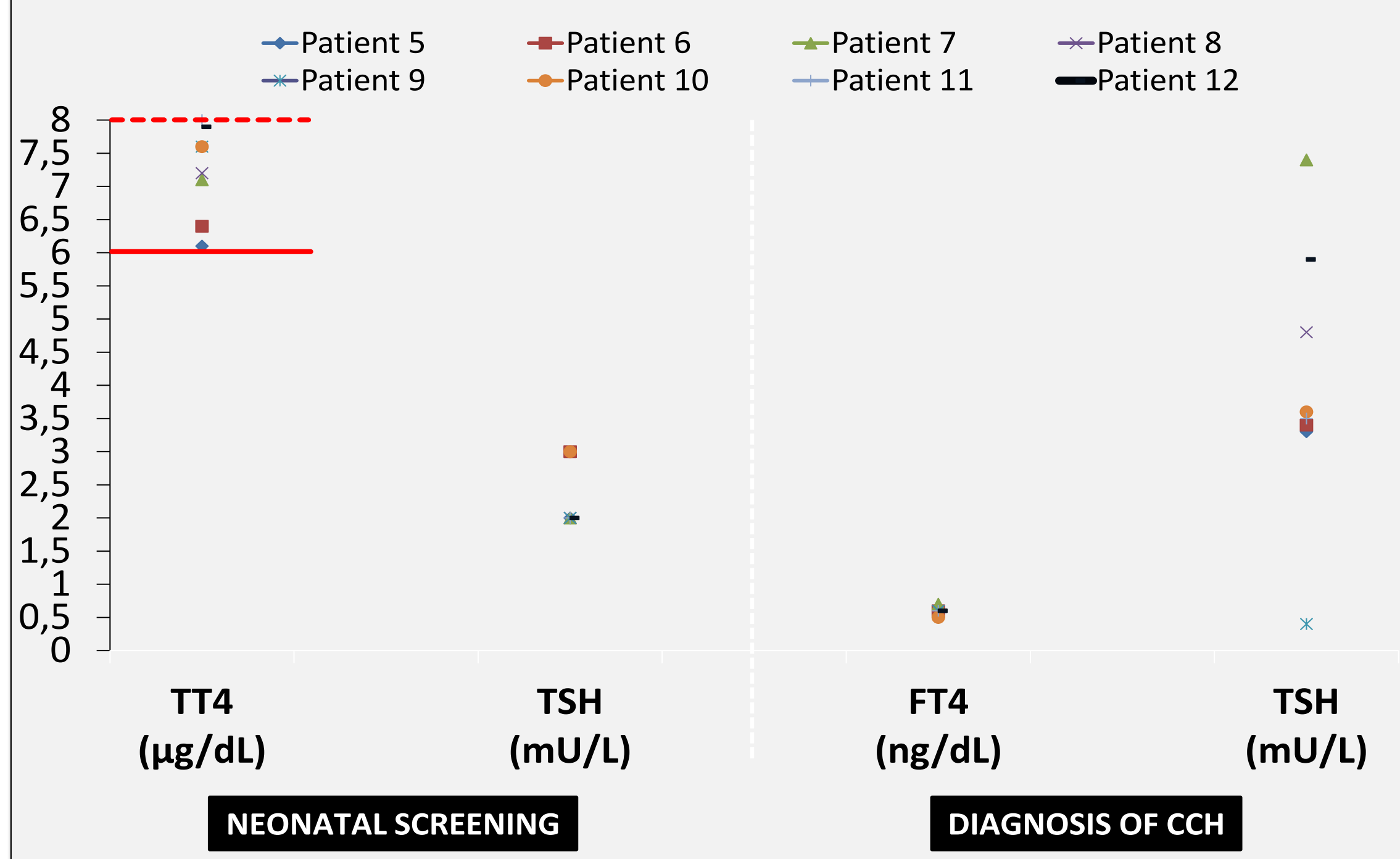
➤ **8 newborns had [TT4] 6-8 µg/dL**
7/8 of patients were diagnosed of AI before 12 months of age, associating clinical symptoms, alterations of the pituitary and/or other hormonal deficits

➤ **6 patients had [TT4] ≥ 8 µg/dL**
Only 1/6 of these patients have AI currently

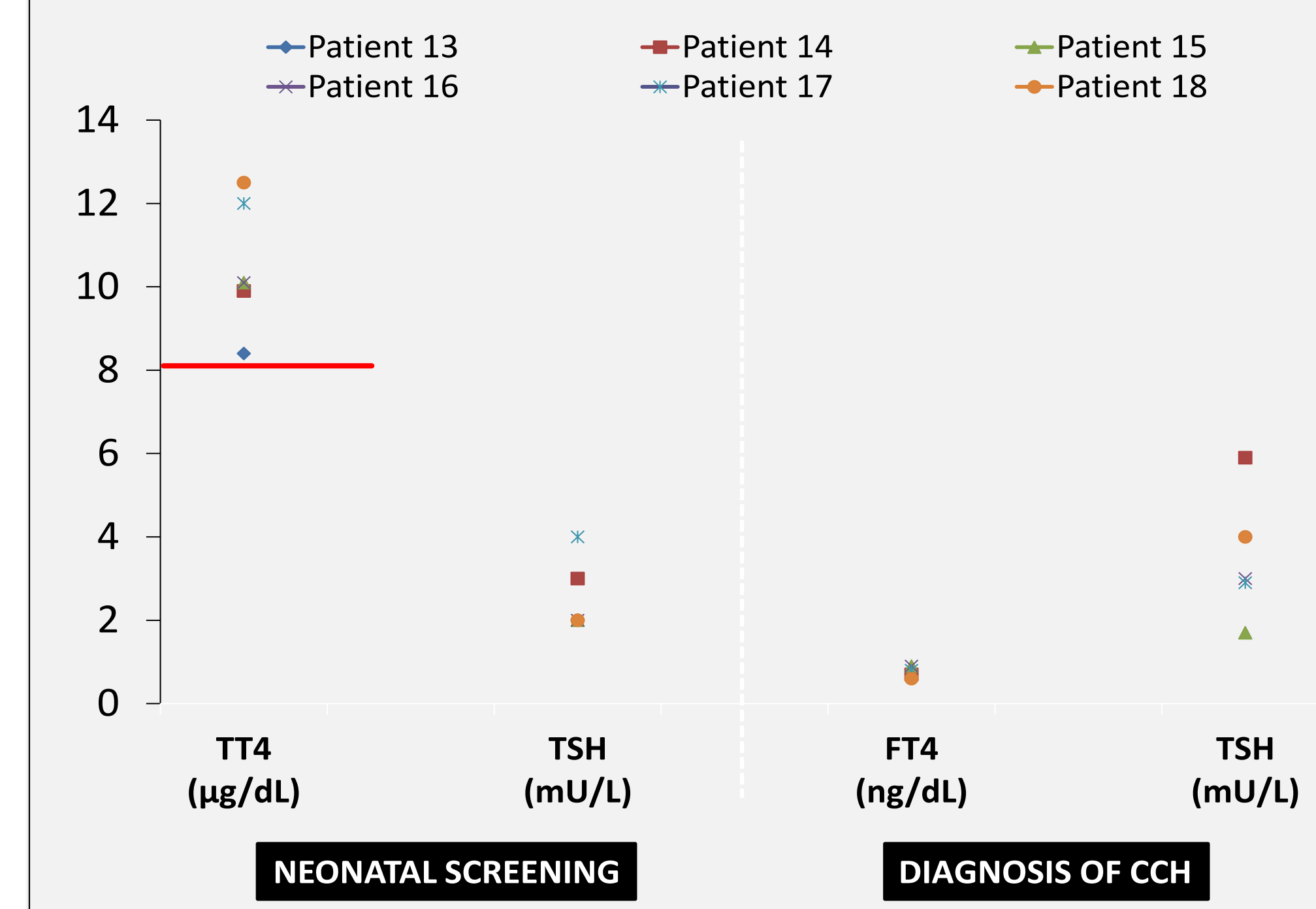
Patients with [TT4] <6 µg/dL in NS



Patients with [TT4] between 6 and 8 µg/dL in NS



Patients with [TT4] ≥ 8 µg/dL in NS



| | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
|------------------|-----------|-----------|-----------|-----------|
| Current age | 20 years | 18 years | 6 years | 15 years |
| Sex | M | F | M | M |
| Getational age | 36 wks | 39 wks | 38 wks | 40 wks |
| Birth weight | 2,300 gr | 2,820 gr | 2,880 gr | 3,380 gr |
| IS | YES | YES | NO | YES |
| IS debut age | < 1 month | < 1 month | - | < 1 month |
| Cortisol (µg/dL) | 1.2 | 0.0 | 12.1 | 1.4 |
| ACTH (pg/mL) | - | - | 14 | 15 |
| DGH | Yes | Yes | Yes | ? |
| Hypogonadism | Yes | Yes | No | No |
| Diabetes insipid | No | No | Yes | No |
| MRI | SOD | PSIS | HAP | HAP |

| | Patient 5 | Patient 6 | Patient 7 | Patient 8 | Patient 9 | Patient 10 | Patient 11 | Patient 12 |
|------------------|-------------------|-----------|-------------------|-----------|-----------|------------|------------|------------|
| Current age | 10 years | 21 years | 8 years | 12 years | 6 years | 12 years | 3 years | 8 years |
| Sex | M | M | M | F | M | M | F | F |
| Getational age | 41 wks | 39 wks | 41 wks | 33 wks | 41 wks | 41 wks | 38 wks | 33 wks |
| Birth weight | 3,670 gr | 3,250 gr | 3,380 gr | 2,600 gr | 3,580 gr | 4,100 gr | 2,190 gr | 2,310 gr |
| IS | YES | YES | YES | YES | YES | NO | YES | YES |
| IS debut age | 9 months | 2 months | 1 year | 4 years | 1 month | - | <1 month | 5 years |
| Cortisol (µg/dL) | 3,4 | 2,5 | 0,0 | 1,7 | 4,4 | 8,5 | 4,0 | 2,1 |
| ACTH (pg/mL) | 17 | 0,0 | - | - | 5,0 | 4,0 | 2,1 | - |
| DGH | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No |
| Hypogonadism | YES Micropenis | - | YES Micropenis | - | - | Yes | No | - |
| Diabetes insipid | No | No | No | No | No | Yes | No | No |
| MRI | PSIS | PSIS | SOD | PSIS | PSIS | PSIS | EPP | SOD |

| | Patient 13 | Patient 14 | Patient 15 | Patient 16 | Patient 17 | Patient 18 |
|------------------|------------|------------|------------|------------|------------|------------|
| Current age | 11 years | 3 years | 16 years | 13 years | 16 years | 18 years |
| Sex | F | M | M | F | M | F |
| Getational age | 36 wks | 40 wks | 41 wks | 41 wks | 39 wks | 39 wks |
| Birth weight | 3,800 gr | 2,710 gr | 3,100 gr | 3,410 gr | 3,045 gr | 3,800 gr |
| IS | NO | NO | NO | YES | NO | NO |
| IS debut age | - | - | - | 5 years | - | - |
| Cortisol (µg/dL) | - | 5 | - | 3.2 | - | - |
| ACTH (pg/mL) | - | - | - | 17 | - | - |
| DGH | Yes | No | Yes | Yes | Yes | Yes |
| Hypogonadism | No | Yes | Yes | Yes | - | Yes |
| Diabetes insipid | No | No | No | No | No | Yes |
| MRI | PSIS | PSIS | PSIS | PSIS | PSIS | PSIS |

CONCLUSIONS:

- The determination of T4 in the NS allowed an early diagnosis of 25% of the CCH, as well as the suspicion of MPDs.
- Most of the MPDs including AI were diagnosed in the first year of life. In all of them, the [T4] in the NS was ≤8 µg/dL. Just considering a clinical point of view, we think it could be interesting to increase the lower cut-off of T4 in our NS.

(1) Horm Res Paediatr 2017. DOI:10.1159/000479367

(2) J Clin Endocrinol Metab 2015;100:E297-300

(3) 1st Edition December 2009. ISBN: 978-84-89342-42-2.Osakidetza.

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