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TSH elevation in neonatal screening as the first manifestation of other associated diseases

Elevación de TSH en el cribado neonatal como primera manifestación de otras enfermedades asociadas

The early detection programme for congenital endocrine and metabolic disease and other diseases screens all newborns. It enables early diagnosis and treatment of different diseases. One of these is congenital hypothyroidism, particularly important due to the involvement of thyroid hormones in brain development, and because it is an avoidable cause of cognitive deterioration.[1,2] Although elevated TSH is usually a marker of primary congenital hypothyroidism,[2,3] it is important to carry out a broad differential diagnosis, as it can be linked to other conditions, as occurred in the two case reports we present here.

Case 1

This was an 18-day-old baby girl who was admitted for jaundice, transient hyperinsulinaemic hypoglycaemia and dehydration, and was found to have elevated TSH on neonatal screening. She was the daughter of young, non-consanguineous parents, who had suffered interruption of the previous pregnancy due to myelomeningocele. Previous medical history: normal pregnancy, emergency Caesarean at 41 + 3 weeks due to abnormal cardiotocography tracing (skullcap pH: 7.18). Anthropometric measurements at birth: weight 3,710 g (SD 0.78), length 50 cm (SD −0.2), head circumference 35.5 cm (SD 0.43). Physical examination normal except for mild macroglossia. While in hospital, the baby had episodes of hypoglycaemia due to transient hyperinsulinism (insulin 8.14 mIU/l in hypoglucaemia, rest of the examinations normal) which required enteral feeding and fluid therapy with a maximum glucose infusion rate of 9 mg/kg/min, resolving at 12 days old. Neonatal screening showed TSH from dried blood spot 9 μU/mL (cut-off point 7 μU/mL); blood analysis: TSH 48.7 mIU/l (normal: 0.72–11); free T4 0.82 ng/dl (normal: 0.93–1.71); free T3 2.82 pg/mL (normal: 2.04–4.4); thyroid-binding globulin (TBG) and thyroid peroxidase (TPO) antibodies negative; thyroglobulin 49.85 ng/mL (normal: 1.4–78). Thyroid scintigraphy showed absence of uptake, and thyroid ultrasound was normal. In view of congenital hypothyroidism, treatment with levothyroxine was started at 13 μg/kg/day. At the age of three months, she developed an irregular left axillary lesion measuring 3 × 1 cm adhered to the overlying skin, initially diagnosed as pilomatrixoma. From the age of six months, she had excessive weight gain, with a weight of 11.3 kg (SD + 3.2), height 68.5 cm (SD + 0.28), which was resolved with dietary measures. At 10 months, a new subcutaneous lesion was found in the left knee and there was a slight drop on the growth chart so, suspecting pseudohypoparathyroidism, blood tests were requested: calcium 9.1 mg/dl (normal: 9–11); phosphorus 5.9 mg/dl (normal: 3.1–6); PTH 614 pg/mL (normal: 15–65); alkaline phosphatase 201 U/l (normal: 0–300); magnesium 2.1 mg/dl (normal: 1.7–2.3); 25(OH) vitamin D 24.8 ng/mL. Urinalysis: normal, calcium/creatinine ratio 0.02, tubular reabsorption of phosphate 87.5%. Genetic study of the *GNAS* gene revealed the heterozygous presence of the pathogenic variant c.293delA, causing a truncated protein (p.Asn93Thrfs*3), confirming the clinical diagnosis of type 1A pseudohypoparathyroidism. The genetic study of both parents was normal, meaning this was a *de novo* variant. Allele-specific RT-PCR studies confirmed that the variant was in the maternal allele.

Case 2

Baby girl referred to the neonatal screening centre at the age of 23 days due to elevated TSH (first sample 10.8 μU/mL, second sample 17.1 μU/mL). Family history: father unknown, mother with unspecified intellectual disability and valvular pulmonary stenosis in childhood. Personal history:

pregnancy without monitoring up to week 26, normal subsequent checks. Normal delivery at 36 weeks. Anthropometric measurements at birth: weight 2,485 g (SD − 0.1), length 46.5 cm (SD − 0.04), head circumference 31 cm (SD − 1.12). Physical examination: anteverted nostrils with prominent eyes, stellate iris, high-arched palate, and II-III/VI systolic murmur in the pulmonary area, the rest normal. Results showed TSH 10.9 mIU/l (normal: 0.72–11), free T4 1.21 ng/dl (normal: 0.9–1.7), free T3 4.8 pg/mL (normal: 2.04–4.4), thyroglobulin 102 ng/mL (normal: 3.5–77), TBG and TPO antibodies negative. Thyroid scintigraphy showed absence of uptake, and thyroid ultrasound was normal. TSH levels persisted at the upper limit of normal, and at the age of six weeks, analysis showed TSH 11.55 mIU/l, free T4 1.28 ng/dl, free T3 4.71 pg/mL. Treatment was started with levothyroxine at 7.5 μg/kg/day, with return to normal of parameters. Echocardiogram: tricuspid pulmonary valve with supravalvular stenosis and maximum gradient of 45−50 mmHg compatible with supravalvular pulmonary stenosis. Suspecting Williams-Beuren syndrome, *array*-CGH was performed, showing a 1.5 Mb deletion in the band 7q11.23 arr[GRCh37] 7q11.23(72,745,047–74,339,044) × 1. The mother has the same alteration, confirming the diagnosis in both. Now (22 months old) the child's laboratory results are normal on levothyroxine 3 μg/kg/day.

Elevated TSH in neonatal screening tests can be the first sign of other diseases. In both cases, absence of uptake was identified in thyroid scintigraphy, with normal thyroid ultrasound and thyroglobulin, with no known reason for the lack of uptake; reports suggest it may be due to iodide uptake-transport defects, acute iodine overload or transient hypothyroidism due to transplacental passage of maternal TSH receptor-blocking antibodies.

In the first case reported, the presence of hypothyroidism in the context of pseudohypoparathyroidism (mainly PHP1A and some cases of PHP1B) was associated with higher TSH levels in neonatal screening, with age at diagnosis similar to that reported by other authors, and the pointers being early weight gain and the development of subcutaneous ossifications,[4–6] as also specified by the international consensus on pseudohypoparathyroidism,[7] in which the diagnosis is established by clinical manifestations. In the first case, clinical suspicion led to the determination of PTH, providing the diagnosis of type 1A pseudohypoparathyroidism, without evidence at that point of the other characteristic laboratory findings, such as hypocalcaemia and hyperphosphataemia.[6] The diagnosis was confirmed after finding a mutation of the *GNAS* gene in the genetic study.[7]

In the second case report, the elevated TSH and the physical examination and echocardiographic findings led us to suspect the diagnosis of Williams-Beuren syndrome, characterised by developmental delay (47.6%), cardiac abnormalities (31%) and facial dysmorphia (5.8%).[8] Supravalvular pulmonary stenosis, as in our case, supravalvular aortic stenosis and mitral valve prolapse are all common. Hypercalcaemia is one of the abnormal blood tests results, but not found in our patient. Neonatal hypothyroidism as the first clinical manifestation is uncommon, although some authors point to an increased prevalence of thyroid disorders at a structural level (hypoplasia or ectopia) and functional level (transient elevation of TSH) as might have occurred in our patient, although the diagnosis is not usually made in the neonatal period, but rather later.[9,10]

In conclusion, elevated TSH in neonatal screening generally means primary congenital hypothyroidism. However, as it can mask an underlying disease, it is important to perform close follow-up and extensive differential diagnosis.

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