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Pilot Neonatal Screening Program for Central Congenital Hypothyroidism: Evidence of Significant Detection

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Keywords

Central hypothyroidism · Congenital hypothyroidism · Congenital hypopituitarism · Neonatal screening program · Dried blood specimen

Abstract

Background/Aim: Congenital hypothyroidism (CH) is a heterogeneous entity. Neonatal screening programs based on thyrotropin (TSH) determination allow primary CH diagnosis but miss central CH (CCH). CCH causes morbidity, alerts to other pituitary deficiencies, and is more prevalent than previously thought. We aimed at developing a pilot neonatal screening program for CCH detection. ***Patients and Methods:*** A prospective 2-year pilot neonatal screening study based on simultaneous dried blood specimen TSH and thyroxine (T_4) measurements was implemented in term newborns aged 2–7 days. Those with T_4 ≤4.5 µg/dL (–2.3 SDS) and TSH <10 mIU/L were recalled (suspicious of CCH) and underwent clinical and biochemical assessment performed by expert pediatric endocrinologists. ***Results:*** A total of 67,719 newborns were screened. Primary CH was confirmed in 24 (1:2,821). Forty-four newborns with potential CCH were recalled (recall rate 0.07%) at a mean age of 12.6 ± 4.8 days. In this group, permanent CCH was confirmed in 3 (1:22,573), starting L-T_4 treatment at a mean age of 12.3 ± 6.6 days; 14 boys showed T_4-binding globulin deficiency (1:4,837); 24 had transient hypothyroxinemia (21 non-thyroidal illness and 3 healthy); and 3 died before the confirmation stage. According to initial free T_4 measurements, CCH patients had moderate hypothyroidism. ***Conclusions:*** Adding T_4 to TSH measurements enabled the identification of CCH as a prevalent condition and contributed to improving the care of newborns with congenital hypopituitarism and recognizing other thyroidal disorders.

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Introduction

Congenital hypothyroidism (CH) is a heterogeneous entity. At birth, most countries effectively screen for primary CH by thyrotropin (TSH) determination [1]. However, this approach misses central CH (CCH), which is caused by disorders of the hypothalamic-hypophyseal system and characterized by impaired TSH production, resulting in low circulating thyroid hormones in combination with low, inappropriately normal, or slightly elevated TSH levels [2]. Although CCH was previously assumed as a rare, mild, and non-relevant disorder, nowadays its spectrum includes an important risk of morbidity, especially when severe cases remain untreated [3, 4].

The main underlying cause of CCH is combined congenital pituitary hormone deficiency (CCPHD), mostly associated with growth hormone (GH) and adrenocorticotropin (ACTH) deficiencies. This may result in recurrent hypoglycemia and acute adrenal insufficiency with impairment of growth and neurodevelopment [2, 5, 6]. Specific symptoms are not usually observed in CCH, and even in those cases where some unspecific clinical findings such as hypoglycemia or cholestasis appear, CCPHD may remain unrecognized during the neonatal period [7].

Different CCH underlying etiologies have been described lately. These include several monogenic disorders such as mutations in thyroid-stimulating hormone beta subunit (*β-TSH*) [3, 8], TSH-releasing hormone receptor defects (*TRH-R*) [9–11], immunoglobulin super family member 1 gene *(IGSF1)* [12, 13], and transducin-like protein 1 X-linked *(TBLX1)* [14]. Each of these has its own clinical and biochemical characteristics, and if no specific study at birth is performed, they are frequently undiagnosed until later [2, 15].

Screening programs that measure thyroxine (T_4) with reflex TSH in newborns with T_4 below a specified cutoff have the potential to detect CCH and have shown a higher prevalence of CCH than previously thought, reaching a rate of 1:16,000 to 1:21,600 [16, 17].

Therefore, the aim of this study was to develop a pilot neonatal screening program adding dried blood specimen (DBS) T_4 determination to our already-based TSH program to determine the incidence of CCH and to evaluate the feasibility and benefits of this strategy.

Patients and Methods

A prospective pilot neonatal screening study based on the simultaneous DBS determination of TSH and total T_4 was conducted from June 1, 2014, to June 1, 2016, in term newborns aged between 2 and 7 days of life in the city of Buenos Aires. During the trial period, newborns with T_4 ≤4.5 μg/dL (–2.3 SDS) associated with TSH <10 mIU/L were suspected of CCH, recalled, and referred to pediatric endocrinologists. All underwent a specific clinical assessment to find CCH signs or symptoms, including concomitant life-threatening comorbidities such as hypoglycemia, dysnatremia, and cholestasis.

Biochemical confirmation tests included a complete evaluation of the pituitary-thyroid axis (serum TSH, T_4, free T_4 [FT_4], triiodothyronine [T_3], thyroglobulin, and antithyroid antibodies) as well as additional pituitary function tests (serum cortisol, prolactin, gonadotropins, testosterone, GH, IGF-I, IGFBP-3, electrolytes, glucose, and liver function). Serum T_4-binding globulin (TBG) determination was performed in patients likely to suffer from TBG deficiency (low T_4 with normal FT_4 and TSH concentrations). Maternal thyroid function was evaluated in all cases. In those patients with confirmed diagnosis of permanent CCH, a brain magnetic resonance imaging (MRI) was requested and molecular study of transcription factors involved in pituitary development was initiated. CH severity was classified according to FT_4 level at confirmation stage [18].

Laboratory Methods

Neonatal DBS TSH was measured by IFMA (Delfia) (intra- and interassay coefficients of variation [CV] 7 and 8%, respectively, for a TSH of 10 mIU/L) with a functional sensitivity of 2 mIU/L. T_4 was measured by FIA (Delfia) (intra- and interassay CV were 7.1 and 4.1%, respectively, for a T_4 of 4.5 μg/dL) with a functional sensitivity of 1.8 μg/dL.

Serum TSH, T_4, FT_4, T_3, thyroglobulin, antithyroid antibodies, cortisol, prolactin, gonadotropins, and testosterone were measured by electrochemiluminescence immunoassay (ECLIA), Cobas e411. GH, IGF-I, and IGFBP-3 were measured by a 2-site chemiluminescence immunometric assay IMMULITE® 2000 system (Siemens Healthcare Diagnostics Products Ltd., Gwynedd, UK). Serum TBG was measured by chemiluminescence.

Genomic analysis of candidate genes (*PROP1, POU1F1, LHX4, LHX3, HESX1, PROKR2, OTX2, SOX3*) was performed by sequencing in each case according to an adapted screening algorithm [19]. All coding exons and intron region boundaries of these genes were amplified from genomic DNA as previously described using exon-flanking primers (sequence posted online) [20].

Statistics

Data were expressed as median and range to describe hormone concentrations and as mean and standard deviation score to express age. Prevalence, recall rates (RR), and costs per detected case were calculated. DBS T_4 levels of diagnostic groups were compared by the Mann-Whitney test. Statistical analyses were performed using GraphPad Prism version 5.01 for Windows (GraphPad Software, San Diego, CA, USA). The alpha level was set at 0.05.

Results

Throughout the study, 67,719 full term newborns were screened by measuring T_4 and TSH simultaneously. A flow chart of the results is shown in Figure 1. Primary hy-

Table 1. Biochemical results of DBS and serum samples at confirmation stage, according to final diagnosis

	n	DBS		Confirmation stage				
		TSH, mIU/L	T_4, μg/dL	TSH, mIU/L	T_4, μg/dL	FT_4, ng/dL	T_3, ng/dL	Thyroglobulin, ng/dL
CCH	3	<2.0	3.00 (2.5–4.5)	3.79 (2.0–7.0)	3.90 (2.19–5.15)	0.56 (0.48–0.77)	76 (56–115)	42.5 (11–74)
HypoTBG	14	2.2	2.52 (1.4–4.1)	4.86 (1.7–10.1)	2.40 (1.54–4.30)	1.52 (0.67–1.96)	56 (43–99)	92.0 (60–219)
NTI	21	<2.0	4.05 (2.2–4.5)	3.97 (0.58–14.4)	10.5 (6.20–20.0)	1.57 (1.19–2.08)	169 (71–219)	29.4 (16–72)
Healthy	3	<2.0	3.80 (3.8–4.1)	3.04 (2.7–4.7)	8.10 (7.6–12.50)	1.63 (1.36–1.92)	137 (111–153)	93.7 (74–112)
Reference values		<10.0	≥4.5	1.3–10	6–18	1.0–2.6	105–325	18–145

Data are presented as median (range). DBS, dried blood specimens; TSH, thyrotropin; T_4, thyroxine; FT_4, free T_4; T3, triiodothyronine; CCH, central congenital hypothyroidism; HypoTBG, thyroid-binding globulin deficiency; NTI, non-thyroidal illness.

pothyroidism was suspected in 135 newborns (RR 0.20%) and confirmed in 24. Forty-four newborns with a potential diagnosis of CCH were recalled (RR 0.07%) at a mean age of 12.6 ± 4.8 days. TSH and T_4 concentrations are shown in Table 1. At confirmation stage, 21/44 (45%) were still hospitalized due to different conditions.

Permanent CCH (median T_4: 3.0 μg/dL; Table 1) was confirmed in 3 cases (2 boys), representing a prevalence of 1:22,573 term newborns. At the time of recall (3, 6, and 19 days of life), all of them were hospitalized with unspecific symptoms such as hypernatremia, recurrent hypoglycemia and suspicion of sepsis. Their pituitary assessment established that CCH was associated with other pituitary hormone deficiencies and with abnormal pituitary findings on MRI (Fig. 2). Molecular studies revealed a sporadic *POU1F1* R271W heterozygous mutation in 1 patient with GH, prolactin, and TSH deficiencies. Thyroid ultrasounds and maternal thyroid function were normal in the 3 cases. L-T_4 replacement was started at a mean age of 12.3 ± 6.6 days. Despite adequate hormone replacement, 1 of these patients died at 0.8 years due to a hypovolemic shock secondary to severe gastroenteritis. The other 2 CCH patients were followed up and underwent a neurodevelopmental evaluation (Gesell maturity scale) at 1.5 years with a normal developmental global score (DQ) of 84 and 100, respectively (Table 2).

Fourteen apparently healthy boys had TBG deficiency (median T_4: 2.5 μg/dL; Table 1, prevalence 1:4,837 newborns), confirmed upon serum TBG determination (non-detectable levels). Fifty percent of mothers revealed serum TBG below the normal range. In this group, 2 patients without comorbid conditions and absence of hypopituitary features had FT_4 levels below the normal range (0.67 and 0.90 ng/dL, respectively), while other pituitary axes were unaffected. In both, isolated CCH was initially assumed, and L-T_4 treatment was initiated with a marked increment of FT_4 without T_4 changes and suppressed TSH. A non-detectable TBG level led to L-T_4 discontinuation at 14 and 3 months, respectively, and thereafter they displayed a typical TBG deficiency pattern (normal FT_4, low T_4, and normal TSH).

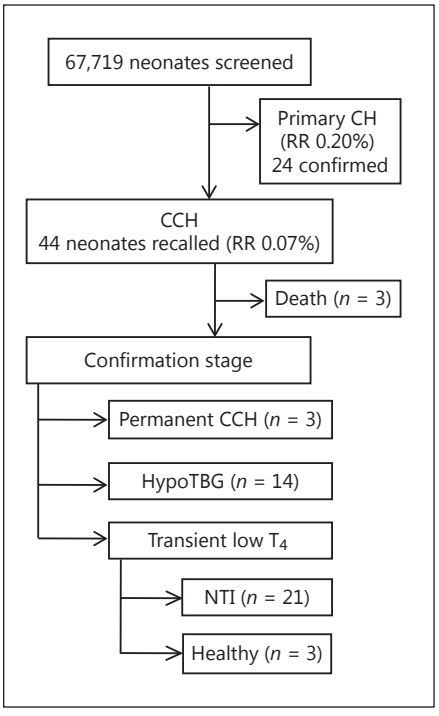

Fig. 1. Overview of simultaneous thyrotropin-thyroxine (TSH-T_4) screening results (flowchart). CH, congenital hypothyroidism; CCH, central CH; TBG, T_4-binding globulin; NTI, non-thyroidal llness.

Table 2. Details of newborns with permanent central congenital hypothyroidism

	Filter paper		Serum samples					Gender	Hormone deficiencies	Brain MRI	Molecular studies	Hormone replacement, days	Follow-up, years
	TSH, mIU/L	T_4, μg/dL	TSH, mIU/L	T_4, μg/dL	FT_4, ng/dL	T_3, ng/dL	Tg, ng/dL						
1	<2.0	3.00	7.07	2.19	0.48	56	11	M	TSH, ACTH, ADH	APH, midline defects	*LHX4*$^{w/w}$ *HESX1*$^{w/w}$	8	Died 0.8
2	<2.0	2.50	3.79	5.15	0.77	115	–	M	TSH, ACTH, GH	APH, ENH, midline defects	*LHX4*$^{w/w}$ *HESX1*$^{w/w}$	20	2.5
3	<2.0	4.5	2.00	3.90	0.59	76	74	F	TSH, GH, PRL	APH	*POU1F1*$^{w/m}$ *R271W, de novo*	9	2.2
	2–10	>4.5	1.3–10	6–18	1.0–2.6	105–325	18–145						

Thyroid profile at screening and confirmation stages, further pituitary assessment, and follow-up. Tg, thyroglobulin; APH, anterior pituitary hypoplasia; ENH, ectopic neurohypophysis. See Table 1 footnote for other abbreviations.

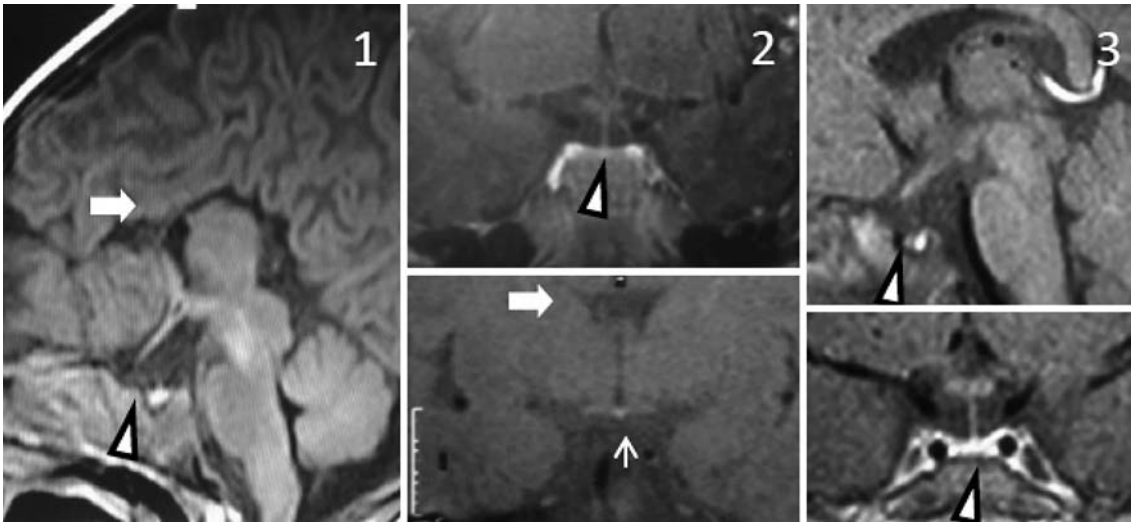

Fig. 2. Brain MRI of the 3 patients with detected central congenital hypothyroidism. Thick arrows show midline defects: corpus callosum agenesia (image 1) and absence of septum pellucidum (image 2); arrowheads: anterior pituitary hypoplasia (images 1–3); thin arrow: ectopic neurohypophysis.

Twenty-four newborns had transient hypothyroxinemia (median T_4: 4.15 μg/dL; Table 1). Twenty-one of them were severely ill at the time of screening and were assumed as having non-thyroidal illness (NTI). Most of those screened were being hospitalized for respiratory distress or sepsis, 1 had a urinary tract infection, and 1 had an isolated transient ACTH deficiency. At confirmation stage, all were markedly or completely recovered with a concomitant increment in their T_4 serum levels. Three of these patients evolved with transient hyperthyrotropinemia (maximum TSH of 14.0 mIU/L), which lasted up to 5 months in 1 patient. One boy first diagnosed with NTI was diagnosed TBG deficiency after overcoming his illness. The remaining 3 neonates with transient hypothyroxinemia were healthy without any known pathological background.

Three newborns who had abnormal T_4 levels on DBS died within the first 2 weeks of life (1 was polymalformated, 1 had complex congenital heart disease, and 1 suffered cardiopulmonary arrest). No confirmation studies were available, and no signs suggestive of CCH were recovered.

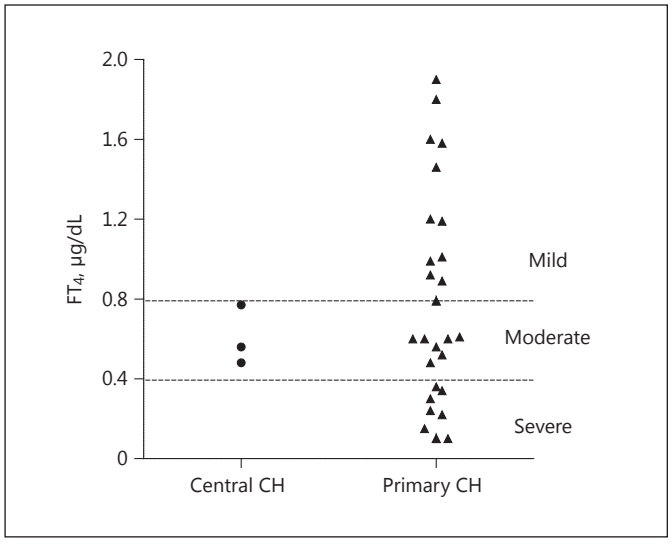

Fig. 3. Severity of FT_4 levels at confirmation stage in central CH and primary CH [18]. CH: congenital hypothyroidism; FT_4, free thyroxine.

The T_4 screened levels in permanent CCH were not significantly different to either transient hypothyroxinemia ($p = 0.39$) or hypoTBGemia ($p = 0.26$). T_4 was significantly lower in the hypoTBG group compared to transient hypothyroxinemia ($p < 0.001$) (Table 1). TSH concentrations (DBS screening) were mostly non-detectable in transient CCH patients and in half of the newborns with TBG deficiency (Table 1).

Based on initial serum FT_4 concentrations, hypothyroidism in primary CH patients (mean age of 13.3 ± 4.8 days) was severe in 9/24 (37.5%), moderate in 7/24 (29%), and mild in 8/24 (33.5%), while in all 3 CCH patients, FT_4 concentrations were in a moderate range (mean age of 9.3 ± 6.9 days) (Fig. 3).

The cost of the TSH-based strategy for primary CH detection was USD 106,996/2 years, meaning USD 4,458 per each detected case. Adding DBS T_4 determination generated an extra cost of USD 2.2 for every screened newborn. Thus, the simultaneous TSH-T_4 determination strategy increased the costs to USD 148,982/2 years, equaling USD 49,661 per each detected CCH patient.

Discussion

Neonatal screening programs are an invaluable public health tool. Created to detect certain congenital diseases, they aim at modifying their deleterious natural course.

They started in the early 1960s and progressively expanded with new determinations to accurately identify and treat metabolic, neurological, and endocrine diseases. Nevertheless, their use in the approach to new diseases should be based on updated information on the disorder, its prevalence, natural course if undetected, available tools for detection, and treatment and cost benefits. [21]. CCH encompasses a group of rare diseases that frequently remains unrecognized during the neonatal period.

In our country and for the last 30 years, the detection of primary CH has been TSH based and has shown good cost-effectiveness. Therefore, in order to detect CCH patients, we undertook this pilot study, adding T_4 to our ongoing TSH-based program during the study period.

This pilot study reveals a relatively high prevalence of CCH (1:22,573), similar to that reported by other studies [16, 17]. In addition, it accounts for 11% of all detected cases of permanent CH. As expected, all the patients with CCH had CCPHD [2]. Only 1 patient exhibited clinical findings that could have suggested a pituitary disorder. The remaining 2 patients did not show a classical phenotype, thus avoiding an early diagnosis as usually occurs with congenital hypopituitarism. It is important to highlight that our patients were diagnosed at an earlier age compared to reported cohorts of congenital hypopituitarism [6, 22, 23].

The implementation of this pilot screening program focused on 2 specific aspects: establishing the T_4 cutoff levels and the relevant role of experienced specialists at the stage of confirmation. CCH may be progressive, and some newborns may only show a moderate decrease in serum T_4 concentrations overlapping normal values. This should be assumed as part of the natural course and severity of the disease rather than a false-negative result of the screening. We studied the normal distribution of T_4 on DBS. Since we did not know in advance the work-up needed to confirm the recalled babies, we choose a T_4 value of –2.3 SDS for a recall level of maximal alert. This strategy requires the clinical skills not only to suspect CCH but also to rule out conditions involving transient central hypothyroidism such as prematurity, born to hyperthyroid mothers, certain drug treatments that suppress the thyroid axis, and NTI. In addition, the search for comorbidities related to CCPHD urges a specific work-up to prevent potential sequelae.

The prevalence of TBG deficiency found in our study was relatively high, similar to that previously reported using DBS or serum neonatal TBG [24, 25]. The unavail-

ability of routine DBS TBG determination in our screening increased the RR in 43%. If available, their work-up would have stopped sooner. Nevertheless, we think these families benefited from this finding as it is usually misinterpreted, leading to erroneous L-T_4 replacement. As described above, TBG deficiency was diagnosed in 2 patients with low FT_4 levels, thus making it difficult to differentiate them from isolated CCH [17]. It is difficult to assess whether they have benefited from transient L-T_4 treatment.

NTI constituted our major cause of recall, similar to other CCH programs. Regarding the 3 neonates who died before the confirmation stage, although they probably suffered NTI, their serum thyroid profile was not available to confirm it.

It has been described that up to 14.5% of recalled babies may have low T_4 without an obvious explanation [16]. In our study, 7% of newborns recalled with probable CCH appeared healthy with no previous pathological conditions known. This figure might vary according to the T_4 cutoff used in each screening program.

The precise clinical impact of TSH deficiency is difficult to ascertain. However, the relevance of this entity is highlighted by the fact that serum T_4 concentrations in CCH did not statistically differ from the levels found in primary CH [18, 26]. In this study, initial FT_4 in CCH newborns were in the range of moderate severity according to the categories previously established for primary CH [18]. Comparing the magnitude of hypothyroidism in patients with CCH and that in the cohort of patients with detected primary CH, we have determined that FT_4 serum levels of CPHD do not significantly differ from eutopic or ectopic primary hypothyroidism. Even though no patients with *β-TSH* deficiency were detected in our study, it is well known that they have severely low FT_4 levels, similar to athyreotic patients [3, 8]. Our experience corroborates that, although thyroid impairment might not be so severe, a prompt diagnosis of CCH allows a timely study of other pituitary hormone deficiencies and associated comorbidities.

According to our results, neonatal screening for CCH fulfills the criteria for disease screening regarding its prevalence, confirmation, and treatment as much as other less prevalent metabolic disorders currently included in many screening programs. To further recommend this strategy, we should optimize its cost-effectiveness, studying larger cohorts and expanding the search for milder forms.

Conclusions

Neonatal T_4 determination allows the identification of CCH as a prevalent condition. Although no studies support that CCH screening is better for detection than clinical presentation, it may improve morbidity and reduce mortality because of unrecognized diagnosis.

We believe that the neonatal screening program based on TSH and T_4 contributes to improving the care of newborns with congenital hypopituitarism and some other hypothalamic-pituitary-thyroidal disorders. Noteworthy, as it fulfils the criteria for disease screening, introducing it into current neonatal screening programs should be considered.

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Statement of Ethics

This study was approved by the local Ethics Committee. Consent for adding T_4 measurement to the current DBS neonatal sample in order to expand the causes of CH was obtained from every maternity ward.

Disclosure Statement

The authors declare no conflicts of interest.

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