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Nationwide Evaluation of Congenital Hypothyroidism Screening during Neonatal Extracorporeal Membrane Oxygenation

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Key Words
Congenital hypothyroidism · Critical illness · Extracorporeal membrane oxygenation · Endocrinology · Euthyroid sick syndrome · Intensive care · Neonatal screening · Neonate · Nonthyroidal illness syndrome · Thyroid hormones

Abstract

Background: Thyroid hormone concentrations may deviate from normal values during critical illness. This condition is known as nonthyroidal illness syndrome (NTIS), and it can influence the results of screening for congenital hypothyroidism (CH) during neonatal extracorporeal membrane oxygenation (ECMO). ***Objectives:*** To determine the incidence of aberrant CH screening results in ECMO-treated neonates, to identify possible determinants, and to follow up patients with abnormal thyroid hormone concentrations. ***Methods:*** In this retrospective cohort study, we included 168 ECMO-treated neonates admitted from 2004 to 2014 and screened by protocol and divided them into the following 3 groups: group 1 (screened during ECMO, n = 107), group 2 (screened shortly before ECMO, n = 26), and group 3 (screened shortly after ECMO, n = 35). ***Results:*** CH screening results were aberrant in 67.3% (72/107) of the neonates screened during ECMO, in 73.1% (19/26) of the neonates screened before ECMO, and in 31.4% (11/35) of the neonates screened after ECMO ($p < 0.001$). Of the neonates with an aberrant screening result, all but 2 (i.e. 98%) had a low thyroxine concentration with a normal thyrotropin concentration at screening, as is seen in NTIS. None was diagnosed with CH. Mortality did not significantly differ between neonates with an aberrant screening result (32.4%) and neonates with a normal screening result (22.7%; $p = 0.18$). Screening before ECMO (OR 5.92; 95% CI 1.93–18.20), screening during ECMO (OR 4.49; 95% CI 1.98–10.19), and a higher Pediatric Logistic Organ Dysfunction-2 score (OR 1.31; 95% CI 1.04–1.66) were associated with an aberrant screening result. ***Conclusions:*** Aberrant CH screening results were found in most ECMO-treated neonates screened before or during ECMO, which is likely due to NTIS. Follow-up of thyroid hormone concentrations is best started after recovery from critical illness. Our results suggest that thyroxine therapy is not required during ECMO.

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Introduction

As thyroid hormones are essential for normal brain development, children with congenital hypothyroidism (CH) are at risk for intellectual disability [1]. CH screening and early treatment have almost eliminated intellectual disabilities caused by untreated CH. In the Netherlands, CH screening is primarily based on thyroxine (T4) screening with supplementary thyrotropin (TSH) and thyroxine-binding globulin measurements aimed at identifying not only children with primary hypothyroidism but also children with central hypothyroidism [2]. However, interpretation of the screening results can be complicated by factors that can transiently reduce thyroid hormone concentrations, such as prematurity [3], drug use [4], cardiac surgery [5], and critical illness [6]. This condition of disturbed thyroid hormone concentrations (low T4 and low triiodothyronine, increased reverse triiodothyronine, and normal or low TSH) during critical illness is referred to as nonthyroidal illness syndrome (NTIS) or euthyroid sick syndrome. It is important to distinguish between CH and NTIS because CH therapy should be initiated as soon as possible, whereas treatment for NTIS is not recommended [6]. In previous studies critically ill neonates have had lower thyroid hormone concentrations than healthy neonates [7–9], and this has been associated with a prolonged hospital stay and a higher mortality [7, 9]. Low thyroid hormone concentrations consistent with NTIS have been found in neonates on extracorporeal membrane oxygenation (ECMO) [10]. However, it is unknown whether ECMO exerts an influence on CH screening results and whether there are any implications of a positive CH screening result during ECMO. We therefore wanted to determine the incidence of aberrant CH screening results in ECMO-treated neonates, identify possible determinants of aberrant screening results, and follow up neonates with abnormal thyroid hormone concentrations.

Materials and Methods

Patients

In this retrospective cohort study, we included ECMO-treated neonates admitted between January 1, 2004, and December 31, 2014, who underwent CH screening in either of the two pediatric ECMO centers in the Netherlands [i.e. Erasmus MC-Sophia Children's Hospital (Rotterdam) and Radboud UMC-Amalia Children's Hospital (Nijmegen)]. These centers use the same entry criteria and treatment protocols, but the prime fluid is different: erythrocyte concentrate is used in the Erasmus MC-Sophia Children's Hospital, and erythrocyte concentrate with fresh frozen plasma (FFP) is used in the Radboud UMC-Amalia Children's Hospital. ECMO was initiated in case of reversible severe respiratory failure with an estimated mortality risk >80% as described by Stolar et al. [11]. The exclusion criteria were: screening not in conformity with the Dutch neonatal screening protocol, incomplete or no screening results available, no registration in the Dutch civil registry (not invited for screening), and ECMO initiated after 8 days of life (not critically ill at the scheduled time of screening). We created the following 3 groups: group 1 (screened during ECMO), group 2 (screened shortly before ECMO), and group 3 (screened shortly after ECMO). Neonates in groups 2 and 3 were considered critically ill at screening, but they did not receive ECMO at that time. CH screening results were obtained from the National Institute for Public Health and Environment (RIVM). In the Netherlands, CH screening is primarily based on T4 measurements by immunochemical blood spots sampled 72–168 h after birth. The method is described in detail in the supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000448238). We classified the initial screening results as either normal or aberrant (abnormal or borderline result on the first heel puncture). In neonates with an aberrant result, the pattern of changes in thyroid hormone concentrations was classified into 3 categories: abnormally low T4 [≤–3.0 SD score (SDS)] with normal TSH (≤7 mU/l), mildly lowered T4 (–3.0 < T4 ≤ –1.6 SDS) with normal TSH (≤7 mU/l), and mildly lowered T4 (–3.0 < T4 ≤ –1.6 SDS) with mildly elevated TSH (7 < TSH ≤ 21 mU/l). Relevant clinical data were collected. The primary diagnosis was defined as the underlying diagnosis requiring ECMO support. Illness severity was estimated using the Pediatric Risk of Mortality III (PRISM III) score [12], calculated for the first 24 h of Pediatric Intensive Care Unit (PICU) stay, and the Pediatric Logistic Organ Dysfunction-2 (PELOD-2) score [13], computed for the 24 h prior to the first heel puncture. Povidone-iodine and radiocontrast materials were not used. Ethical approval was obtained from the local ethics committees (CMO 2005/253).

Follow-Up of Neonates with Abnormal Thyroid Hormone Concentrations

Follow-up serum free T4 (FT4) and TSH concentrations were obtained from the medical charts of neonates with an abnormal CH screening result. FT4 and TSH were compared to the reference values established by Lem et al. [14]. An abnormal value was defined as <–2 SDS or >+2 SDS compared to the reference values.

Data Analysis

Data are expressed as means ± SD, medians (IQR), or numbers (%), as appropriate. Categorical variables were compared using the χ^2 test or Fisher's exact test. Student's t test or a one-way ANOVA was used for normally distributed variables, and the Mann-Whitney U test or the Kruskal-Wallis test was applied for non-normally distributed variables. To correct for multiple testing, the Bonferroni correction was used, and adjusted p values are given. Univariate logistic regression analyses served to identify associations between clinical variables [primary diagnosis, time of screening (before/during/after ECMO), PRISM III score, PELOD-2 score, and drug usage] and aberrant screening results. Use of the following intravenous drugs ≤8 h prior to screening was recorded: dopamine, dobutamine, furosemide, morphine, fentanyl, and hydrocortisone. From a few hours after administration, these drugs can temporarily affect thyroid hormone concentrations; pretreatment levels are reached within hours after discontinuation of the drug [4, 15–19]. Variables with $p \leq 0.20$ were included in the multiple logistic re-

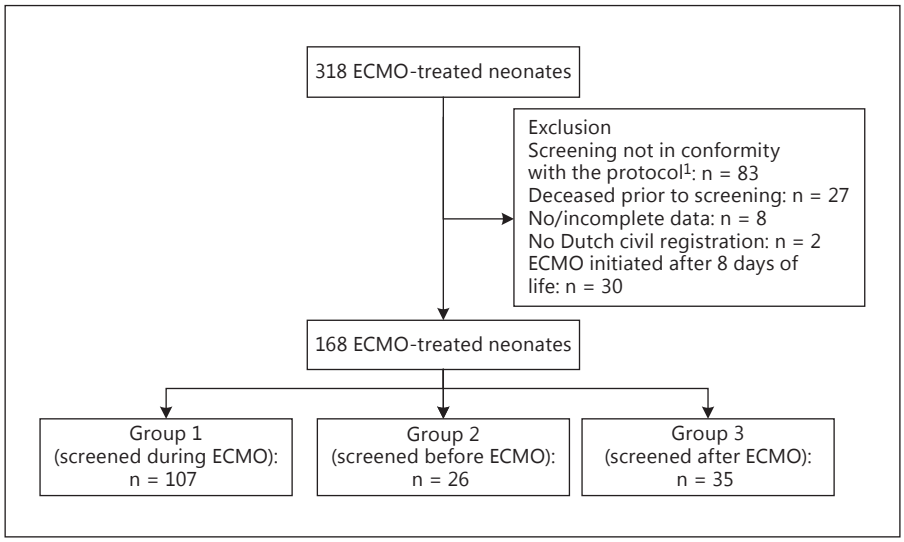

Fig. 1. Flowchart of the study population. [1] Screening performed too early (n = 1) or too late (n = 82).

Table 1. Patient characteristics

	Group 1 (n = 107)	Group 2 (n = 26)	Group 3 (n = 35)	p value
Gestational age, weeks	39.9 (38.1–41.0)	40.0 (37.0–41.0)	40.4 (39.0–41.1)	0.21
Birth weight, g	3,247±631	3,256±704	3,541±595	0.06
Male sex	62 (57.9)	17 (65.4)	20 (57.1)	0.77
Primary diagnosis				0.08
Meconium aspiration syndrome	41 (38.3)	9 (34.6)	17 (48.6)	
Congenital diaphragmatic hernia	35 (32.7)	6 (23.1)	5 (14.3)	
Sepsis	11 (10.3)	3 (11.5)	5 (14.3)	
Persistent pulmonary hypertension	10 (9.3)	6 (23.1)	8 (22.9)	
Other[1]	10 (9.3)	2 (7.7)	0 (0)	
Age at the start of ECMO therapy, days of life	1 (0–2)	6 (5–7)	1 (0–1)	<0.001
Duration of ECMO therapy, days	7 (5–9)	6 (4–7)	3 (2–4)	<0.001
PRISM III score (first 24 h of PICU admission)	17 (15–23)	17 (9–21)	17 (12–21)	0.12
Age at CH screening, days of life	4 (4–5)	4 (4–4)	6 (5–7)	<0.001
PELOD-2 score (24 h prior to CH screening)	6 (6–7)	5 (5–7)	6 (5–7)	0.03

Data are expressed as means ± SD, medians (IQR), or numbers (%). [1] Congenital heart disease, congenital cystic adenomatoid malformation, recurrent pneumothoraces, infant respiratory distress syndrome in combination with pneumothorax, meconium peritonitis, respiratory failure of unknown cause.

gression analysis. Multicollinearity was not found. Data were analyzed using SPSS 21.0 for Windows (IBM Corporation, Armonk, N.Y., USA). Statistical significance was accepted at the 5% level.

Results

Patients

ECMO was initiated in 318 neonates (fig. 1). We included 168 neonates divided into 3 groups. Table 1 shows the patient characteristics. In group 3, ECMO was started later, and CH screening was performed later. Further, the duration of ECMO therapy was shorter in group 3. The median PELOD-2 score was higher in group 1 than in group 3 (adjusted p = 0.045). Eight patients received levothyroxine therapy (online suppl. table 2). Three of them had a normal initial screening result and developed hypothyroxinemia later, which was identified by routine laboratory tests. One patient was diagnosed with thyroid dyshormonogenesis and required lifelong treatment.

Table 2. CH screening results

	Group 1 (n = 107)	Group 2 (n = 26)	Group 3 (n = 35)
Initial screening			
Normal result → no further action	35 (32.7)	7 (26.9)	24 (68.6)
Abnormal result → referral[1]	42 (39.3)	10 (38.5)	5 (14.3)
Abnormally low T4, normal TSH[2]	42	10	5
Dubious result → second screening	30 (28.0)	9 (34.6)	6 (17.1)
Mildly lowered T4, normal TSH[3]	28	9	6
Mildly lowered T4, mildly elevated TSH[4]	2	–	–
Second screening			
Died before the second screening	1	0	0
Normal result → no further action	22	9	6
Abnormal result → referral[1]	7	0	0
Abnormally low T4, normal TSH[2]	1	–	–
Mildly lowered T4, normal TSH[3]	2	–	–
Mildly lowered T4, mildly elevated TSH[4]	4	–	–

[1] To a pediatrician for further analysis. [2] T4 ≤–3.0 SDS and TSH ≤7 mU/l. [3] –3.0 < T4 ≤ –1.6 SDS and TSH ≤7 mU/l. [4] –3.0 < T4 ≤ –1.6 SDS and 7 < TSH ≤ 21 mU/l.

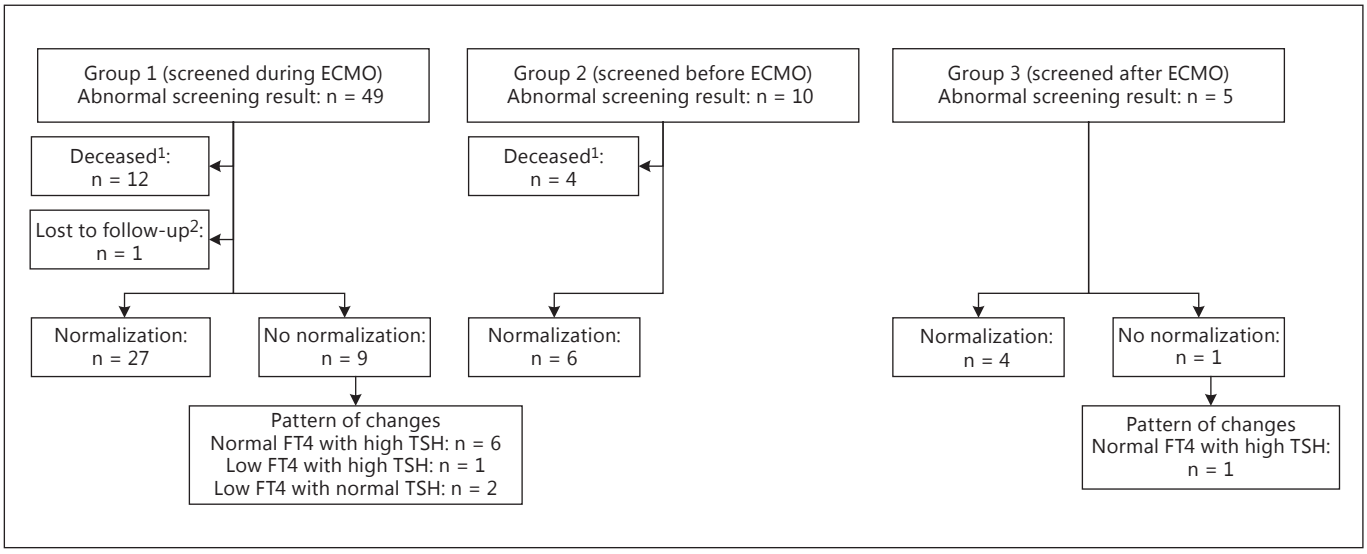

Fig. 2. Follow-up of neonates with abnormal screening results. [1] Deceased before follow-up of thyroid hormone concentrations was performed. [2] Transferred to another hospital.

CH Screening Results

Table 2 shows the screening results. The incidence of aberrant results was higher in group 1 (67.3%) and group 2 (73.1%) than in group 3 (31.4%; both adjusted p < 0.001). At the initial screening, the combination of low T4 and normal TSH was found in 100 of 102 neonates (table 2). Neonates with an aberrant screening result were treated longer with ECMO and had higher PELOD-2 scores than those with a normal screening result (online suppl. table 3). The incidence of aberrant screening results in group 1 in both centers was similar and thus irrespective of the use of FFP in the prime fluid (67.2% with

Table 3. Results of logistic regression analyses: clinical variables associated with an aberrant screening result

	Univariate model	p value	Multivariate model[1]	p value
Time of screening				
After ECMO (ref.)	1.00	–	1.00	–
Before ECMO	5.92 (1.93–18.20)	0.002	4.59 (1.11–18.93)	0.04
During ECMO	4.49 (1.98–10.19)	<0.001	3.19 (1.22–8.32)	0.02
PELOD-2 score	1.31 (1.04–1.66)	0.02	1.27 (0.99–1.63)	0.06
Primary diagnosis				
Meconium aspiration syndrome (ref.)	1.00	–	1.00	–
Congenital diaphragmatic hernia	1.78 (0.82–3.89)	0.15	1.41 (0.60–3.34)	0.44
Others	1.51 (0.73–3.13)	0.27	1.34 (0.56–3.16)	0.51
Dopamine				
No (ref.)	1.00	–	1.00	–
Yes	1.63 (0.84–3.18)	0.15	1.01 (0.46–2.21)	0.98
Morphine				
No (ref.)	1.00	–	1.00	–
Yes	1.98 (0.75–5.19)	0.17	1.60 (0.54–4.73)	0.40

Values are presented as OR (95% CI). ref. = Reference. [1] Adjusted OR, adjusted for all other variables shown in the table.

FFP vs. 67.3% without FFP; p = 1.00). The proportion of aberrant screening results in group 1 was not dependent on the time elapsed between the start of ECMO and blood sampling for CH screening (data not shown).

Follow-Up of Neonates with Abnormal Thyroid Hormone Concentrations

The follow-up results are shown in figure 2. Sixteen neonates died before the follow-up was initiated, and 1 was transferred to another hospital. Thyroid hormone concentrations normalized in 37 neonates at the median age of 10 days (IQR 8–17.5). In 29 of those neonates, this happened before 28 days of life; thyroid hormone concentrations normalized in the other 8 neonates between 30 and 108 days of life. Normalization of thyroid hormone concentrations could not be confirmed in 10 children (fig. 2). At the last follow-up, low FT4 values ranged from 12.0 to 12.7 pmol/l and high TSH values ranged from 5.7 to 14.9 mU/l in these children.

Aberrant CH Screening Results and Mortality

The mortality rate before hospital discharge was 28.6% (48/168). The mortality rate was not significantly higher in children with an aberrant CH screening result (32.4%) than in children with a normal screening result (22.7%; p = 0.18).

Associations between Clinical Variables and an Aberrant CH Screening Result

In the univariate logistic regression analyses, screening before ECMO, screening during ECMO, and a higher PELOD-2 score were significantly associated with an aberrant screening result (table 3). In the multivariate model, screening before and during ECMO remained associated with an aberrant screening result.

Discussion

More than two thirds of the initial CH screening results were aberrant in ECMO-treated neonates screened before and during ECMO. Low T4 in combination with a normal TSH concentration was found in all but 2 neonates with an aberrant screening result, which normalized rapidly without treatment in most cases. None of these children was diagnosed with CH. This suggests that aberrant screening results are due to NTIS, and that levothyroxine therapy during ECMO is not required. The incidence of aberrant screening results in the group of neonates screened after ECMO was significantly lower than that in the 2 other groups, possibly reflecting that clinical recovery occurs during ECMO.

Reduced thyroid hormone concentrations have been found in critically ill term neonates treated with or without ECMO [7–10]. The effect of neonatal ECMO on thy-

roid hormone concentrations has been studied only by Stewart et al. [10]. They found a decline in all thyroid hormone concentrations directly after the start of ECMO in a cohort of 14 neonates, which suggests a dilutional effect. Additionally, Agus and Jaksic [20] reported that thyroid hormone concentrations in ECMO prime fluid were significantly below normal. They suggested that these concentrations would be even lower in prime fluid without FFP [20]. However, in the present study the incidence of aberrant screening results was not higher in the center without FFP in the prime fluid. Although we acknowledge that the occurrence of hemodilution after ECMO cannulation plays a role in the lowering of thyroid hormone concentrations, we think that NTIS contributes more to this, and that hemodilution may further lower thyroid hormone concentrations in critically ill neonates. This assumption is supported by our finding that the incidences of aberrant screening results did not significantly differ between screening before (73.1%) and during (67.3%) ECMO.

Screening before and during ECMO and a higher PELOD-2 score were associated with an aberrant screening result. Further, neonates with an aberrant screening result had higher PELOD-2 scores than neonates with a normal screening result, suggesting an influence of illness severity. Nevertheless, the use of the PELOD-2 score has some limitations. Though validated for a broad group of PICU patients [13], its performance in ECMO-treated neonates is unknown. Further, the PELOD-2 score is affected by treatment. Therefore, we cannot firmly conclude that illness severity plays a role in causing aberrant screening results.

Dopamine has been found to suppress TSH in previous studies [17, 19], but we did not find an association between dopamine and an aberrant screening result. Therefore, dopamine does not seem to be the main cause of aberrant CH screening results. However, our study does not allow pinpointing of the exact effect of dopamine on thyroid hormone concentrations.

Now, clinicians will be most concerned with the implications of aberrant CH screening results. As we found a lower risk of aberrant screening results in neonates screened after ECMO, follow-up of thyroid hormone concentrations should be started after ECMO and ideally after recovery from critical illness. However, because T4 treatment should not be started later than the first 2 weeks of life to prevent intellectual disabilities [21], we recommend that thyroid function tests be repeated before this age.

The consequences of low thyroid hormone concentrations during critical illness remain controversial. Correlations between low thyroid hormone concentrations and adverse outcomes have been found, including increased mortality [8, 9, 22]. We did not find a significant difference in mortality rates between neonates with an aberrant screening result and neonates with a normal screening result. However, it should be noted that our sample size was small, and the results could have been biased by the lack of screening results for the 27 neonates who died before screening was performed.

As thyroid hormones are essential for early brain development, transiently reduced thyroid hormone concentrations during early life could affect neurodevelopment, which has been shown in premature infants [23, 24]. In that case, supplementation of thyroid hormones during NTIS could be beneficial. On the other hand, a recent study in young adults did not confirm this association between transient hypothyroxinemia of prematurity and adverse neurodevelopmental outcomes [25]. Furthermore, neonatal T4 supplementation was not beneficial in premature infants [26]. As levothyroxine therapy has not been proven to be beneficial, and thyroid hormone concentrations normalized rapidly in most cases, we do not advise starting levothyroxine therapy in ECMO-treated neonates based on an aberrant screening result in the first 2 weeks of life.

To our knowledge, this is the first study reporting on CH screening results in ECMO-treated neonates with follow-up of thyroid function. A strength is the use of an efficient CH screening method. Further, this is the largest cohort study investigating CH screening results in ECMO-treated neonates. Limitations are its retrospective design, its small sample size, and the lack of a strict schedule to follow up abnormal thyroid hormone concentrations. The small sample size does not allow drawing of a strong conclusion about the influence of the time of sampling during ECMO on screening results. Further, the exact date of normalization in some patients with abnormal thyroid hormone levels remains uncertain.

In conclusion, we found a higher incidence of aberrant CH screening results in neonates screened before (73.1%) or during (67.3%) ECMO than in neonates screened after (31.4%) ECMO. All but 2 neonates (i.e. 98%) with an aberrant screening result had low T4 concentrations with normal TSH, as is seen in NTIS. Thyroid hormone concentrations normalized rapidly in most, and none of these children was diagnosed with CH. Our results suggest that T4 therapy is not required during ECMO. Follow-up of abnormal thyroid hormone concentrations is best performed after recovery from critical illness.

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Disclosure Statement

The authors have no competing interests.

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