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Non-thyroidal illness in critically ill children

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Abstract

Purpose: This review summarizes recent literature on non-thyroidal illness syndrome (NTI) and outcome of pediatric critical illness, to provide insight in pathophysiology and therapeutic implications.

Recent findings: NTI is typically characterized by lowered triiodothyronine levels without compensatory TSH rise. Although NTI severity is associated with poor outcome of pediatric critical illness, it remains unclear whether this association reflects an adaptive protective response or contributes to poor outcome. Recently, two metabolic interventions that improved outcome also altered NTI in critically ill children. These studies shed new light on the topic, as the results suggested that the peripheral NTI component, with inactivation of thyroid hormone, may represent a beneficial adaptation, whereas the central component, with suppressed TSH-driven thyroid hormone secretion, may be maladaptive. There is currently insufficient evidence for treatment of NTI in children. However, the recent findings raised the hypothesis that reactivation of the central NTI component could offer benefit, which should be tested in RCTs.

Summary: NTI in critically ill children can be modified by metabolic interventions. The peripheral, but not the central, component of NTI may be a beneficial adaptive response. These findings open perspectives for the development of novel strategies to improve outcome of critical illness in children.

Key words: Non-thyroidal illness, pediatrics, critical illness, outcome.

1. Introduction

Critical illness in children admitted to the pediatric intensive care unit (PICU) is associated with substantial neuroendocrine and metabolic changes [1]. The acute stress induced by critical illness generates a shift in energy expenditure and alterations in the balance between anabolism and catabolism [2], in which the hypothalamic-pituitary-thyroid (HPT) axis plays a critical role. Pronounced HPT axis changes typically develop, in both children and adults, referred to as non-thyroidal illness syndrome (NTI) [3,4]. Most characteristic of NTI are decreased T3 levels, without a compensatory rise in TSH. The peripheral component of NTI is hallmarked by an increased conversion of circulating T4 to the biologically inactive reverse T3 (rT3), whereas its conversion to biologically active T3 is decreased, contributing to a reduced peripheral bioavailability of active thyroid hormone at the organ level [5]. In the central component of NTI, the pituitary does not respond to the decreased plasma thyroid hormone levels as it does in healthy circumstances, as TSH levels are inappropriately normal or low.

In the pediatric population, NTI mostly has been described in critically ill children after cardiac surgery [6-10], but also in critically ill children with sepsis or septic shock [11-14], diabetic ketoacidosis [15], or oncological problems [16,17]. Since NTI also occurs during fasting in healthy circumstances, to reduce energy expenditure to limit catabolism [18,19], it can also be seen in adolescents with anorexia nervosa [20,21]. In critically ill children, the severity of NTI has been associated with worse clinical outcome [11,14,22-24]. However, it remains unclear whether this association reflects an adaptive protective response or contributes to poor outcome. This review summarizes insight in the pathophysiology of this syndrome and the relation of non-thyroidal illness syndrome with clinical outcome of critical illness, to reflect on possible implications for treatment.

2. Pathogenesis of non-thyroidal illness

The pathogenesis of NTI has only partly been unraveled but affects both central and peripheral levels (Figure 1).

At the hypothalamic level, TRH expression is suppressed. Animal models showed a decreased TRH mRNA expression in the paraventricular nucleus after acute inflammation [25], chronic inflammation [26], and prolonged critical illness [27]. Local hypothalamic T3 bioavailability rather than circulating thyroid hormones may contribute to this suppression. The expression of type 2 deiodinase (D2), which regulates local thyroid hormone availability in the brain, is increased in rodent and rabbit NTI models [27-29]. *In vitro*, D2 activity in human glioma cells increased T3 production, which induced T3-responsive genes in co-cultured neurons [30]. However, in a rabbit NTI model, increased hypothalamic D2 expression did not coincide with elevated local T3 concentrations [27]. Other factors that may contribute to the suppressed TRH expression include glucocorticoids and interleukin-1 beta (IL1 β), which are both endogenously increased during critical illness [31,32]. In rats, corticosterone and dexamethasone treatment [33] and central infusion of IL1 β [25] profoundly reduced TRH mRNA in the hypothalamic hypophysiotropic neurons.

TSH levels are transiently elevated but rapidly return to normal in the acute phase of illness when measured in a single daytime sample [34]. Studies in adult patients have shown that the normal nocturnal TSH surge is already absent, though, and that in the prolonged phase of critical illness pulsatile TSH secretion is virtually completely lost [35]. Low TSH mRNA expression has been observed in the pituitary of animal models [26,28]. The underlying mechanism of the inappropriately low TSH secretion by the pituitary remains unclear. Increased D2 activity in the pituitary, converting local T4 into T3 and thereby suppressing TSH secretion by feedback inhibition, may theoretically play a role but has not been proven [36]. In addition, the cytokine-induced increase in D1 expression in the pituitary may contribute [37,38]. Cytokines also directly suppressed TSH secretion in pituitary cell cultures [39,40].

Also changes at the level of the thyroid gland contribute to NTI. Indeed, increased circulating levels of cytokines affect different levels of the thyroid hormone synthesis pathway, resulting in a down-regulation

of T4 and T3 secretion. Studies in cultured thyrocytes have shown suppressive effects of IL1 α , IL1 β , IL6, IFN γ or TNF α on thyroglobulin expression and secretion, iodide uptake by the sodium/iodide symporter (NIS), ¹²⁵I incorporation in thyroid hormone, and thyroid peroxidase expression [41].

Finally, several changes in peripheral thyroid hormone availability occur. The metabolism of thyroid hormone is changed, through altered expression and activity of the deiodinating enzymes, possibly mediated by cytokines [41,42] and hypoxia [43]. D3 expression, which is virtually absent in healthy individuals, was shown to be induced in the liver and skeletal muscle of critically ill adults who died [44]. This upregulation results in more conversion of T4 to the biologically inactive rT3. In contrast, the hepatic expression and activity of the T3-producing enzyme D1 was decreased [44,45]. Together, the changes in deiodinase activity diminish the T3 availability. Altered thyroid hormone transporter and thyroid hormone receptor expression also affect thyroid hormone activity. Finally, in critically ill children with meningococcal sepsis, lower T4 levels have been related to lower thyroxine-binding globulin (TBG) levels, both associated with disease severity [14]. Decreased binding could therefore also contribute to the altered peripheral thyroid hormone availability [5].

Apart from the above-described endogenously modified pathways of NTI in critical illness, iatrogenic effects on thyroid hormone secretion and metabolism should be considered. Indeed, drugs commonly used in the PICU can iatrogenically influence TSH secretion. Glucocorticoids suppress TSH release from the thyrotropes through inhibition of TRH secretion in the hypothalamus [46-49]. Also dopamine, often infused for inotropic and vasoactive support in the PICU, suppressed TSH secretion in pediatric critically ill patients [50]. Rat studies suggested that opioids affect the TRH-stimulated TSH release [51] but studies in humans revealed conflicting results [52-54]. Less commonly used drugs in PICU such as anti-epileptic medications including carbamazepine, oxcarbazepine and valproic acid, may also alter pituitary responsiveness to TRH [49,55,56]. Finally, iatrogenic iodine intoxication, via iodine containing contrast fluids or antiseptics and dressings, may also affect thyroid hormone availability and TSH secretion [57].

3. Association of non-thyroidal illness with outcome

Several observational studies have investigated associations of HPT axis hormone changes in critically ill children with clinical outcome.

With regard to T4 and its peripheral conversion to T3 or rT3, these studies show largely similar results. In a heterogeneous cohort of 588 critically children, a lower serum T4 level and a lower T3/rT3 ratio upon admission were independently associated with a delayed live discharge from PICU [23]. A study in 44 children who survived meningococcal septic shock showed that a low baseline T4 was independently associated with a longer PICU stay [13]. Several small studies in critically ill children and neonates with sepsis showed an association of low T3 and low T4 levels with mortality [11,14,22,58]. A large study in 980 critically ill children showed that a low T4 upon admission was independently associated with a higher 90-day mortality and with a higher risk of acquiring a new infection in PICU [24]. A lower upon admission T3/rT3 ratio was independently associated with a longer PICU stay and a higher risk of acquiring a new infection.

The association between TSH and clinical outcome is less clear. Two small studies observed higher TSH levels upon PICU admission in non-survivors than in survivors of meningococcal sepsis (n=26) [59] or septic shock (n=24) [60]. However, in larger studies of heterogeneous cohorts of critically ill children, TSH concentrations upon PICU admission were not associated with mortality, PICU length of stay or acquisition of a new infection [23,24]. Several factors may explain the different findings apart from varying medical conditions requiring PICU admission. First, TSH levels are transiently elevated immediately after the onset of the illness [34]. Thus, TSH levels could have differed depending on the time point of serum sampling in the process of critical illness. Second, as described above, iatrogenic confounders on TSH secretion during PICU stay can also play a role.

4. Impact of metabolic interventions on non-thyroidal illness in relation to outcome

Although the association between the severity of NTI and worse clinical outcome in critically ill children is well established, an association does not clarify whether NTI is a beneficial or harmful response to critical illness. Two studies investigating the impact of a randomized metabolic intervention in PICU on the changes in the thyroid axis in relation to acute clinical outcomes have shed some light on this aspect. The first study was a preplanned subanalysis of a large RCT performed in 700 critically ill children aged 0-16 years who had been randomized to tight glycemic control (TGC) with intensive insulin therapy or to usual care [23]. In the TGC group, insulin was infused to control blood glucose levels within age-adjusted normal fasting ranges (50-80 mg/dl for infants younger than 1 year, 70-100 for older children) [61]. In the usual care group, insulin infusion was started only when the blood glucose level exceeded 215 mg/dl, and stopped when glycemia fell below 180 mg/dl. TGC decreased morbidity and mortality of critically ill children as compared with usual care, despite an increased incidence of hypoglycemia [61]. NTI was present upon PICU admission in both patients groups [23]. However, the peripheral component of NTI further aggravated over time in the TGC group as compared with the usual care group (Figure 2), reflected by a more pronounced further lowering of the T3/rT3 ratio from admission towards day 3 of PICU stay (or last day of PICU stay if patients had a shorter stay). The more pronounced peripheral inactivation of thyroid hormone may be explained by the lower blood glucose levels with TGC that are mimicking a fasting response [23]. The further lowering of the T3/rT3 ratio statistically explained part of the clinical benefit of TGC [23]. This suggests that the peripheral component of NTI may be a beneficial adaptation to critical illness in children. In critically adults undergoing a similar intervention [62], TGC did not affect the critical illness-associated changes in thyroid hormones [63], possibly explained by selection of long-stay patients only.

A second large RCT, investigating the effect of withholding early supplemental parenteral nutrition (PN) in critically ill children [64], showed a similar and even more pronounced effect on the critical illness-

induced thyroid axis changes [24]. This RCT randomized 1440 critically ill children, aged 0-17 years, to receiving supplemental PN within 24 hours after admission (“early PN”) when enteral nutrition alone failed to reach caloric targets, or to not receiving such supplemental PN during the first week in PICU (“late PN”) which created a macronutrient deficit [64]. Children in the late PN group recovered faster and acquired fewer new infections in PICU as compared with children in the early PN group. A preplanned subanalysis showed that NTI was present upon PICU admission in both patient groups, and that late PN further lowered the T3/rT3 ratio from admission towards day 3 or last PICU day for patients with a shorter PICU stay (Figure 2). Although TSH levels were unaffected, low T4 levels, reflecting at least partially the consequence of the central component of NTI, further decreased in the late PN group whereas they increased in the early PN group [24]. The more pronounced mimicking of a fasting response by withholding macronutrients in combination with lower blood glucose levels may explain why the randomized intervention in this RCT had a greater impact, with an additional aggravation of NTI at the central level, reflected by the further T4 lowering, as compared with TGC in fed conditions. The further aggravation of the peripheral component of NTI by late PN, reflected by the further lowering of the T3/rT3 ratio, statistically contributed to the outcome benefit of late PN. Again, this finding suggests that the peripheral inactivation of thyroid hormone in NTI may be a beneficial response. Interestingly, as the further lowering of T4 by late PN statistically counteracted the outcome benefit, the central component of NTI may be interpreted as a harmful response to critical illness in children. These findings confirm the results of a secondary analysis [65] of a similar RCT in adult critically ill patients receiving early-PN (initiation of supplemental PN within 48 hours after ICU admission) or late-PN (supplemental PN withheld during the first week in ICU) [66].

In summary, in relation to whether NTI is a beneficial or a maladaptive response to critical illness, these new findings suggest that the central and the peripheral components of NTI should be considered separately, as the central component appears harmful, whereas the peripheral component appears beneficial.

5. To treat or not to treat non-thyroidal illness?

Over the last decades, treatment of NTI in an attempt to improve clinical outcome in critical illness has been the subject of controversy [67,68]. Treatments with T3, T4 and TRH have been suggested. In critically ill adults, effects of T3 treatment on outcome have been inconsistent. T3 treatment of cardiac surgery patients reduced peripheral vascular resistance and increased cardiac output in 2 RCTs [69,70], but did not improve clinical outcome in several other RCTs [71-73]. T3 treatment of burn injury patients did not affect mortality as compared with placebo therapy [74]. Recently, T3 infusion in mechanically ventilated patients with NTI who had failed a spontaneous breathing trial did not improve respiratory muscle function [75]. In critically ill children, RCTs on T3 treatment have only been performed after cardiac surgery with cardiopulmonary bypass (Table 1) [76-81]. In most RCTs, T3 treatment was not associated with differences in length of PICU or total hospital stay. In one RCT, T3 infusion improved myocardial function and reduced the need for postoperative intensive care [78]. However, these results could to some extent have been biased since the patients were also infused with dopamine, an important iatrogenic suppressor of the thyroid axis in critically ill children [50]. The multicenter TRICC (Triiodothyronine Supplementation in Infants and Children Undergoing Cardiopulmonary Bypass) RCT in critically ill children younger than 2 years old showed no effect of T3 infusion on time to endotracheal extubation in the entire study population, but suggested a potential benefit in children younger than 5 months [76]. To specifically evaluate safety and efficacy of T3 infusion in this age group, the TRICC-2 trial is currently ongoing (Clinical Trials.gov, NCT02320669). A single center RCT of a similar design as the TRICC RCT, showed that oral T3 treatment shortened time to extubation, particularly in infants aged 5 months or younger [77]. Although hypothyroidism in children specifically raises concerns about neurodevelopment [82], T3 treatment in children after cardiopulmonary bypass with NTI did not improve neurodevelopmental outcomes [83]. Of concern is the associated suppression of circulating TSH levels after T3 administration [77] which could theoretically hamper the recovery of the pituitary TSH secretion in NTI. Since no studies

are available on T3 administration in diagnostic groups other than cardiac surgery, and excessive levels of T3 can be harmful [84], also recommendations on T3 treatment in other groups of critically ill children cannot be made. RCTs investigating T4 treatment are only available in critically ill adults and showed no effect on outcome [85] whereas one study showed even an increased mortality in the treatment group [86]. T4 administration also suppressed TSH secretion [85,86] and in view of the decreased conversion of T4 to T3 during critical illness further investigating its effect on outcome may not have a high priority. The recent insights that the central component of NTI could be harmful [23,24] raise the hypothesis that reactivation of the central component of NTI by infusing TRH could possibly be beneficial. Theoretically, this would seem a safer option than treatment with T4 or T3. Indeed, the negative feedback exerted by thyroid hormones on the pituitary thyrotropes would be maintained, avoiding too high levels of thyroid hormones, and adaptive peripheral inactivation of thyroid hormone would be able to proceed as needed. In prolonged critically ill men, continuous infusion of TRH increased thyroid hormone levels but also increased rT3 [87]. When TRH infusion was combined with a GH-secretagogue, the normalization of thyroid hormones occurred without an increase in rT3 [88] explained by a suppressive effect of GH on D3 activity [89]. The impact of such treatment with hypothalamic releasing factors on outcome of critically ill children remains to be investigated.

6. Conclusion

Critical illness-associated NTI is common in children. Despite substantial progress, the underlying pathophysiological mechanisms remain incompletely understood. The well-established association of the severity of NTI with worse outcome of critical illness in children re-opened the dialogue on whether or not NTI should be treated in an attempt to improve clinical outcome. Two metabolic interventions that improved outcome of critically ill children, namely targeting age-adjusted fasting glucose levels and withholding early supplemental PN in PICU, have shown to further aggravate NTI over the first days in PICU. Statistical explanatory analyses suggested a maladaptive role for the central component of NTI

and a beneficial role for the peripheral inactivation of thyroid hormone in NTI. Hence, although a recent RCT showed potential benefit of T3 infusion in a selected patient group of critically ill infants younger than 5 months after cardiac bypass surgery, these data suggest a potential benefit of treating the central rather than the peripheral component of NTI. Therefore, future RCTs should investigate the effect of administering hypothalamic releasing factors on outcome of critically ill children given that such releasing factors could preserve the body's negative feedback loops and the regulation of peripheral metabolism of thyroid hormones and as such protect against inappropriately high thyroid hormone levels.

Key points

- Critical illness in children is associated with several neuroendocrine alterations. The changes in the HPT axis are referred to as the non-thyroidal illness syndrome (NTI), most typically characterized by low circulating T3 levels without a compensatory rise in TSH. The severity of NTI in critically ill children has been associated with worse clinical outcome.
- Two recent studies on metabolic interventions in the PICU that affected the critical illness-induced NTI and improved outcome suggested that the peripheral component with inactivation of thyroid hormone may represent an acutely beneficial adaptation whereas the central component may be a maladaptive response to critical illness.
- It should be further investigated whether treatment of the central component of NTI with hypothalamic releasing factors could improve outcome of critical illness in children, given that such an intervention allows the adaptive peripheral inactivation of thyroid hormone to take place.

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Conflicts of interest

There are no conflicts of interest.

Figure legends

Figure 1

Heading: Overview of the pathogenesis of NTI

Legend: The pathogenesis of NTI involves alterations at various levels of the HPT axis. Potential underlying mechanisms at each level are illustrated. D1: deiodinase type 1; D2: deiodinase type 2; D3: deiodinase type 3.

Figure 2

Heading: The effect of tight glycemic control (TGC) versus usual care (UC) and of the early versus late administration of parenteral nutrition (PN) on the HPT axis.

Legend: Bars (mean $\pm$ standard error of the mean) represent the changes (referred to as Δ) from the admission values to day 3 in PICU (or to the last day for patients with shorter PICU stay) in serum thyrotropin (TSH), thyroxine (T4), triiodothyronine (T3), reverse T3 (rT3) and the T3/rT3 ratio. P-values are obtained with multivariable analysis after adjustment for baseline risk factors (upon-admission diagnosis, age, and severity of illness with PeLOD score for usual care versus tight glycemic control, and

upon-admission diagnosis, age, treatment center, risk of malnutrition with STRONGkids score, and severity of illness with PeLOD and PIM2 score for early versus late PN).

PeLOD, Pediatric Logistic Organ Dysfunction score; STRONGkids, Screening Tool for Risk On Nutritional Status and Growth; PIM2, Pediatric Risk of Mortality 2 score.

Table 1

Heading: Overview of RCTs in critically ill children evaluating the effect T3 treatment on clinical outcome

Legend: CPB: cardiopulmonary bypass; TISS: therapeutic interventional scoring system; VSD: ventricular septal defect

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• of special interest

•• of outstanding interest

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