Endocrine diseases in the newborn. The vision of a neonatologist

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ABSTRACT

Endocrine disorders in the neonate, even if rare, could lead, if undetected, to preventable death or lifelong neurological consequences. This paper reviews special situations when the neonatologist should investigate a possible endocrine deficiency. We discuss three possible scenarios: the neonate with dysmorphic features or malformations that suggest a syndrome associated with endocrine deficiency (usually of the pituitary gland or hypothalamic-pituitary axis), the infant with positive screening test (usually a positive screening test when investigations and treatment are urgent). Special attention is given to the trickiest situation when an endocrine disease could occur: an unusual presentation of a normal neonatal condition. Two situations are discussed: prolonged jaundice, in which hypothyroidism or ACTH deficiency should be investigated, and persistent and prolonged hypoglycemia when congenital hyperinsulinism could be the cause. We provide clues to the diagnosis and treatment of this condition. As a take-home message for the neonatologist, endocrine disorders are conditions that should be known and promptly recognized, especially in the case of unusual presentations of different neonatal pathologies.

Keywords: endocrine disorders, neonate, hypothyroidism, jaundice, hypoglycemia

INTRODUCTION

Neonatology represents a subspecialty of pediatrics that studies the care of the infant during the first 28 days of life [1]. It can be divided into three branches:
• Delivery room resuscitation and sustaining the transition to extrauterine life
• Care of the normal neonate
• Diseases specific to the newborn [2].

Even if hormonal influences, primarily cortisol [3], thyroid [4], and insulin [5], play an important role in the transition to extrauterine life, neonatal endocrinology is a domain many neonatologists neglect. With limited space in the neonatology textbooks [6-8], endocrine diseases of the neonate could present in many ways and, if unrecognized or untreated, can result in death and lifelong consequences [4,5].

This paper serves as an update on neonatal endocrinology, providing insights from the perspective of a neonatologist. It is not intended to be comprehensive, as certain complex conditions like the adrenogenital syndromes warrant a separate, in-depth discussion. The focus of this paper will be on reviewing pathologies of the hypophysis, thyroid, pancreas, and adrenal glands, particularly those that can mimic other neonatal diseases.

When should we investigate a possible endocrine problem in a neonate?

There are a couple of situations in which an endocrine investigation is necessary in a neonate:
• Dysmorphic features or malformations that suggest a syndrome associated with endocrine deficiency
• Positive screening test
• Unusual presentation/evolution of a common neonatal condition.
Dysmorphic features or malformations associated with an endocrine deficiency

The first situation is a syndrome with dysmorphic features or malformations when an endocrine deficiency is expected. This is the case, especially in patients with cerebral malformations – midline defects – agenesis of the corpus callosum, and agenesis of the septum pellucidum, in which case a septo-optic dysplasia is to be excluded [9,10]. This syndrome in this situation, the protocol includes the determination of the concentration of the hormones produced by the anterior pituitary gland [10], but postnatal imaging should be performed in any case of a patient with antenatal identified such malformations in order to visualize the optic chiasm and the pituitary gland [9,10]. MRI is the procedure of choice; the technique could offer images of the optic chiasm and pituitary gland besides visualization of the septum pellucidum and colossal body. Although MRI images offer a good and standardized view, the head ultrasound could identify in the fetal life both the optic chiasm [11-13] and the pituitary gland [12] in transverse trans-temporal sections. Those sections have also been used in adult medicine to identify pituitary tumors [12]. Another situation where endocrine investigations could be necessary is craniofacial malformations, cases in which pituitary deficiency should also be investigated [9]. This is explained by the origin of the common embryologic origin of the anterior pituitary and certain facial structures [9].

Another situation of a syndrome in which endocrine problems are expected is that of the syndromes associated with thyroid dysfunction [14]. Hypothyroidism can be a feature in the case of trisomy 21, CHARGE syndrome, and also Williams syndrome [14]. Consequently, in the case of identifying these diseases, the thyroid function should also be investigated (see below). The reciprocal relation is also true – in the case of congenital hypothyroidism, the incidence of congenital anomalies is three times higher than in the general population [14], most of the cases being malformation of the heart and great vessels [15] or urinary tract anomalies [16].

Positive screening test

The second situation when an endocrine condition should be investigated is the neonate with a positive screening test, the most encountered such situation being that of a positive thyroid screening test result. There are at three methods of neonatal thyroid screening [14, 17-19]:

- Concomitant screening of TSH and Free T4.

In order to understand the value and the limitations of these tests, a discussion about thyroid, the pre- and postnatal evolution of the thyroid hormones is necessary. The thyroid gland produces two hormones: thyroxine (T4) and triiodothyronine (T3) [4]. The secretion of these hormones is controlled by the anterior pituitary gland by TSH – the decrease of thyroid hormones leads to an increase in TSH and their increase diminishes the production [14]. The fetal thyroid gland begins to produce hormones after the 10th week of gestation [14]. The maternal thyroid hormones cross the placenta, so the fetus with hypothyroidism is not usually affected before delivery since the concentrations of T4 are 1/2-1/3 of the normal ones due to the trans-placental passage of maternal hormones [14]. After delivery, in a normal-term neonate, a brisk increase of TSH determines an increase in the production of thyroid hormones by the neonatal gland [4]. This increase occurs during the first hours after birth, at 60-08 mIU/L, and the TSH concentration decreases to normal during the following 5 days [20]. This is why the neonatal screening for thyroid deficiency by determining the TSH concentration is best performed at 48-72 hours [14,17-19]. There are situations where the TSH increase occurs after the first day of life, such as in premature neonates. Premature infants have lower T4 serum levels in the first days of life, proportional to the degree of prematurity, and also have a reduced increase in the levels of TSH [14]. The causes for this situation are multiple – first, the lower amount of T4 that crosses the placenta, the immaturity of the thyroid gland, and the control mechanisms by the hypothalamic-pituitary-thyroid axis [4,14]. Also, two conditions of transitory decreased thyroid hormone levels should be known and recognized in preterm and sick neonates in order to differentiate them from congenital hypothyroidism:

- Euthyroid sick syndrome – a condition with a transient alteration in the thyroid function associated with non-thyroidal illness – found mainly in premature neonates with respiratory distress syndrome and consisting of low levels of T3 associated with normal levels of T4 and TSH – the name euthyroid is given by the fact that the TSH levels are normal [4]. The usual screening programs do not detect this transitory condition, with no long-term effects

- Transient hypothyroxinemia of prematurity – the levels of T4 are low, but the TSH levels are normal, probably due to an immaturity of the hypothalamic-pituitary-thyroid axis [4]. The condition is also transitory and not detected by the usual screening programs.
As previously mentioned, in Romania, the screening method used for the assessment of TSH determines the risk of hypothyroidism followed, in the case of a low value, by the confirmatory determination of Free T4 [21]. The test is performed best after 48 hours to avoid the physiologic increase in TSH, which can result in false positive results. In the case of a TSH > 20 mIU/ml, the neonate is referred to an endocrinologist for the continuation of the investigations and appropriate therapy [21]. Communication between doctors of different specialties is essential because referral of a baby with a positive screening test should be quick in order to begin substitution therapy before the age of two weeks [14,21]. Initiation of the treatment in the first two weeks, before the hormone deficiency, will determine irreversible neurologic consequences and avoid the appearance of neurologic deficits in neonates with congenital hypothyroidism [14,21].

Although there are situations in which the neonatal screening could be normal (like the central hypothyroidism due to pituitary deficiencies in which TSH will be normal or low – so the screening test would be normal), T4 and free T4 will be low, and the thyroid hormones deficiency will be present) or the screening will be done incorrectly – during the first 24 hours in patients discharged early from the maternity hospital or patients admitted in the Neonatal Intensive Care Unit and transfused – in which case the screening is performed before transfusion) or premature infants that have other normal values than term neonates and other evolution of the thyroid hormones). Moreover, the patient could develop later a thyroid hormone deficiency [14]. This is why a high index of suspicion is needed in certain cases of neonatal usual pathology, which will be detailed further.

**Unusual presentation/evolution of an usual neonatal condition**

The first two situations presented above are explicit. However, the last one, which will be discussed further, is tricky for a neonatology beginner because it represents usual neonatal conditions in which “things do not go as expected.” The main topics that will be discussed are neonatal jaundice and neonatal hypoglycemia. Neonal hypocalcemia, which could be associated with parathyroid gland abnormalities, will not be covered in this paper.

**Neonatal jaundice** is normal, occurring in more than 80% of the neonates [1,6,7]. In normal-term newborns, neonatal jaundice begins after 24 hours of life, attains a peak on the day of life 3, and diminishes on the day of life 5 [6,7]. This is due to the shorter duration of life of the erythrocytes, which are a primary source of bilirubin, and the relative and temporary immaturity of the glucuronic-conjugation system in the liver [6,7]. Premature infants have a particular form of jaundice that begins later (after a day of life 3), peaks on the day of life 5, and begins to fade on the day of life 7, being present for a couple of weeks [6,7]. In these cases, the total bilirubin values rarely go over 12-15 mg/dl, and the values more than 20 are not usually present [22].

<table>
<thead>
<tr>
<th>Condition</th>
<th>Special features/ clues</th>
<th>Possible endocrine problem</th>
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<tbody>
<tr>
<td>Jaundice</td>
<td>Prolonged&lt;br&gt;Associated features – large posterior fontanel, enlarged tongue, goiter, neurologic symptoms (hypotonia, lethargy), hypothermia&lt;br&gt;Presence of a syndrome&lt;br&gt;Trisomy 21&lt;br&gt;CHARGE syndrome</td>
<td>Congenital hypothyroidism</td>
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<td></td>
<td>Prolonged jaundice&lt;br&gt;Cholestatic jaundice</td>
<td>Isolated ACTH deficiency</td>
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<td>Hypoglycemia</td>
<td>Prolonged – more than 48-72 hours&lt;br&gt;Hypoketotic – decreased betahydroxibutirate&lt;br&gt;Needs large amounts of iv glucose to maintain a normal glucose value – 10 -12 mg/kg/min&lt;br&gt;Large for gestational age (LGA)&lt;br&gt;Dysmorphic features (Beckwith-Wiedemann syndrome – see text)</td>
<td>Congenital hyperinsulinism</td>
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<td>Low cortisol level</td>
<td>Congenital adrenal insufficiency, congenital hypopituitarism</td>
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<td>Neonatal sepsis</td>
<td>No risk factors&lt;br&gt;Fulminant onset&lt;br&gt;No response to antibiotics&lt;br&gt;Associated with hypoglycemia, other metabolic abnormalities</td>
<td>Congenital adrenal deficiency (primary or secondary)</td>
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are many causes of pathologic jaundice in the neonate, some related to hemolysis (blood type incompatibility, membrane or enzymatic defects of the erythrocytes), some related to different degrees of deficit of the conjugation pathways in the liver (Rotor, Crigler Najar syndromes), intra-uterine or perinatal infections, inborn errors of metabolism [6,7,22]. Many of these causes are more frequent than endocrine problems. However, two endocrine causes should be investigated in the case of neonates with prolonged or particular presentations of jaundice after excluding a more frequent cause – hypothyroidism and ACTH deficiency.

**Hypothyroidism** could be indeed the cause of prolonged jaundice, even in the case of negative screening results [14]. This is the reason why the American Academy of Pediatrics suggested in 2023 that TSH and free T4 should be measured and steps taken accordingly, regardless of a negative screening test result in a neonate, if there is a prolonged jaundice that could not be explained otherwise [14,17]. This could be the case because of a delayed form of hypothyroidism or a hypothyroidism part of a chromosomal or malformative syndrome. One should not forget, though, that there are cases of transitory hypothyroidism encountered in premature or sick neonates (see above) that need no treatment. The risk of hypothyroidism is increased in the case of concomitant presence of other clinical signs suggestive of this disorder: large posterior fontanel or tongue, goiter, constipation, hypothermia, or neurologic symptoms like hypotonia or lethargy[14]. A thyroid function test in this situation does not cost much. However, if the result is positive and the treatment is administered in a timely manner, this represents a correctable cause of the neurologic deficit. The development of the child would be normal. A delay in diagnosis could lead to lifelong consequences. This is why, in the case of a prolonged jaundice or a jaundice in which the cause and gestational age of the child do not justify the evolution, thyroid function testing is mandatory.

**Cholestatic jaundice** could be caused, among other factors, by **isolated ACTH deficiency** [10]. The explanation for this is the action of the cortisol to increase bile flow [10]. In the case of cholestatic jaundice due to ACTH deficiency, hypoglycemia (the lack of cortisol, a hormone that determines the increase of blood glucose – not counter-balancing the effects of insulin) and failure to thrive (an unsatisfactory weight gain) are also associated [10]. Because of a lack of circadian rhythm variations, only the cortisol determination is insufficient for the diagnosis [10]. Instead, a low ACTH concentration and a deficient ACTH response to the administration of CRH are required for the diagnosis [10,12]. It is very important to timely diagnose this condition in a neonate with cholestatic jaundice and hypoglycemia because a delay in diagnosis could lead to the death of the patient due to not receiving the appropriate treatment [23].

Particular cases of **hypoglycemia**, especially prolonged hypoketotic hypoglycemia, are another situation when we have to consider an endocrine problem, especially hyperinsulinism [24-26] and cortisol deficiency [10]. In order to understand this concept, one must re-consider all the knowledge about the definition and mechanisms for hypoglycemia in the neonate. The most convenient definition of hypoglycemia relies on blood glucose values – under certain values, the hypoglycemia is affirmed [27,28] or the Whipple triad [24,27]. The truth is that a correct definition of hypoglycemia is that of a glucose value that has neurologic consequences [24]; in this case, the value depends on the availability of secondary oxidative substrates like ketone bodies, and this makes the target glucose value different for different mechanisms and diseases [24-26]. Classical textbooks teach that hypoglycemia in the neonate occurs by three mechanisms: decreased reserves (like in small for gestational age –SGA or premature neonates), increased consumption (acute neonatal conditions, sepsis, perinatal asphyxia) or hyperinsulinism (large for gestational age infants or infants of diabetic mothers) [27,28]. Research, however, shows us that hyperinsulinism is the mechanism of occurrence of hypoglycemia in the neonate, and the temporary or permanent character of the anomaly can give clues about the etiology [24-26]. The temporary forms of hyperinsulinism without endocrine component are transitional hyperinsulinism and perinatal stress hyperinsulinism [25,26]. These forms are caused by transitory deficiencies of expression of the potassium channels responsible for insulin secretion and are self-limited to the first 24-48 hours of life [25,26]. Endocrine-mediated hyperinsulinism is represented by the genetic forms of hyperinsulinism (congenital hyperinsulinism) responsible for persistent or late-occurring hypoglycemia[25,26]. These forms are responsible for the rare causes of endocrine-mediated hypoketotic hypoglycemia and are characterized by late-onset or persistence beyond 48-72 hours of life [25]. The reason for the transient forms of hyperinsulinemia in the neonate is represented by the low threshold glucose value for insulin secretion – in order to begin the secretion of insulin, a much lower value of blood glucose should be reached in the immediate neonatal period; also, there is a lower expression of the potassium-dependent trans-membrane channels that are involved in the regulation of the insulin secretion, due to perinatal hypoxia and other neonatal conditions [25,26]. This situation resolves by 48 hours of life, so hypoglycemia in the breastfed neonate older
than 48 hours is usually hyperketotic and thus not associated with hyperinsulinism [26].

There are several characteristics of endocrine-mediated hyperinsulinism. First, there is hyperketotic hypoglycemia – i.e., the beta-hydroxy-butyrate levels are low, and this means that there is no alternative substrate available for the brain in case of a decreased amount of glucose [24-26]. In this case, the target glucose value (the value that prevents irreversible brain damage) is considered to be higher than in other situations – that means a value > 70 mg/dl [24]. The clinical clue for this condition is represented by the persistence of hypoglycemia beyond 48 hours of life (during the day of life 3), a time when, in other cases, the transitory causes of hyperinsulinism would have resolved[25,26]. As a consequence, any hypoglycemia in a neonate that is persistent beyond 48 hours should be suspected to involve a persistent, congenital, genetically determined hyperinsulinism [25,26] and should be managed accordingly:

- The target blood glucose value should be > 70 mg/dl because the patient is suspected not to have alternative fuels available, and the risk for brain lesions in this case is important [24]
- The treatment should involve oral feeding (breastfeeding, formula, oral glucose gel) and iv. glucose because hyperinsulinism determines a significant, continuous decrease in glucose value, and oral, intermittent feeding is insufficient to maintain normal blood glucose [24]. Indeed, the necessary glucose consumption rate for a neonate is 4-6 mg/kg/minute, equal to the rate of breakdown of hepatic glycogen [27], and the glucose needed in order to maintain normal blood glucose is often > 10-12 mg/dl in the patients with congenital hyperinsulinism; this need is another clue to the congenital and permanent nature of the condition
- In the case of persistent hypoglycemia, it is mandatory to exclude congenital panhypopituitarism by determining the levels of cortisol (greater than 10 micrograms/ml) and growth hormone (greater than 7 nanograms/ml) [25]
- The alternative treatments for cases with persistent hypoglycemia should be well chosen. Even if this is tempting, glucocorticoid treatment should not be used in the case of persistent hypoglycemia [24,26]. Cortisol is a hormone that increases blood glucose levels, but the treatment is insufficient to produce a good rise in glucose and could cause adverse effects [24]. Instead, glucagon could be attempted, but the administration is intermittent, and the effect also [24] – high rate glucose infusion remains the cornerstone of the treatment [24]. Because of their role in insulin secretion, potassium dependent channels could be manipulated in order to decrease hyperinsulinism, and this task could be accomplished by using a trial of diazoxide [25]. After 72 hours of progressive-increasing treatment, diazoxide should decrease and eliminate the need for IV glucose infusion to maintain a normal blood glucose level [25]. If this is not accomplished, a genetic cause involving probably a defective potassium channel is probable [24,25]
- Investigating the cause of congenital hyperinsulinemia is often difficult and should be accomplished by specialist endocrinologists who have to be consulted in this case. It involves testing the efficacy of a diazoxide trial (as previously mentioned), looking for clinical clues that can establish the etiology like large for gestational age newborn, macroglossia and splanchномегали that are the features of Wiedemann Beckwith syndrome or imaging of the pancreas with 18-Fluoro-L-3,4-dihydroxyphenylalanine PET scan, in order to identify if this is a generalized pancreatic disfunction or just islands of defective tissue – fact that will change both the principle of surgical intervention and the prognosis [25]. Genetic testing is also available and could identify mutations in different locations involved in insulin secretion [25,26]: ABCC8 and KCN11 genes that code the structure of the subunits of K potassium channel, CGK and GLUD 1 (glutamate dehydrogenase 1), mutation in the transcription factor genes for the potassium channels [26]. Testing for these anomalies is elaborate, takes time, and is not involved in the immediate management of the infant (except for identifying cases not responsive to diazoxide). It could be performed later in infancy.

Another unusual presentation is that of the primary or secondary adrenal insufficiency, that can mimic neonatal sepsis and, if undetected, could result in the death of the patient in the absence of appropriate treatment [30]. As previously mentioned, these conditions will not be discussed in the present review.

Even if hyperinsulinemia is an important cause of persistent hypoglycemia in the neonate, care should be taken not to overlook other causes like metabolic diseases with onset in the neonatal period [29]. The same is true in the case of unexplained neonatal jaundice [29]. Though, the metabolic disorder resulting in prolonged hypoglycemia and jaundice in the neonatal period are not the topic of this paper and will not be discussed here, the reference provided above represents a good information source.

**CONCLUSIONS**

Although rare, endocrine disorders in the neonate should be always in the differential diagnosis of many
signs and symptoms. Endocrine deficiencies, especially of the pituitary gland, should be investigated in the case of malformation syndromes, in particular those with craniofacial malformations and midline defects. A positive screening test (increased TSH value) is always an alarm sign and will be followed by confirmatory investigations and treatment. And, most of all, an unusual presentation and/or prolonged course of common neonatal condition like jaundice or hypoglycemia should alert the clinician to the possibility of a un-detected hypothyroidism or ACTH deficiency in the case of jaundice or a congenital hyperinsulinism in the case of hypoglycemia.

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