Congenital Hypothyroidism and Transient Thyrotropin Excess: Differential Diagnosis of Abnormal Newborn Thyroid Screening

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ABSTRACT

This article reviews the current knowledge of both transient and long term abnormalities of the newborn pituitary-thyroid axis. These defects are grouped according to their presenting characteristics in the neonatal screening programs. Some of the controversies regarding etiology, pathophysiology, and possible treatments are discussed.

Introduction

With the accumulation of large amounts of information regarding thyroid function from newborn screening programs, new variations and abnormalities of the pituitary-thyroid axis function, both transient and on-going, have been identified. The total incidence of these entities approaches one in 5,000 live births (excluding those restricted to premature infants), thus representing a number roughly equal to the incidence of congenital primary hypothyroidism. Thus, the clinician has been presented with an increasingly complex differential diagnosis based on the results of the now routine newborn thyroid screen. In this article, these entities will be reviewed in the format of the differential diagnosis of abnormal thyroid screening test results.

Thyroid Development and Ontogenesis

Fetal thyroid development can be divided into three distinct phases: embryogenesis, hypothalamic maturation, and, finally, development of the thyroid-pituitary feedback inhibitor system.23 Abnormalities in any of these phases result in distinct clinical entities which may be picked up on the newborn thyroid screen.

The developing fetal hypothalamic-pituitary axis develops independently of maternal thyroid environment in all but a few situations.2,5 As in other mammals, the human placenta appears virtually impermeable to maternal iodothyronines: tri-

* The views of the author are his own and do not purport to reflect the position of the Department of the Army or the Department of Defense.
iodothyronine (T3), thyroxine (T4) and reverse T3 (rT3).\textsuperscript{1,2,4,6,17,21,46} Further, thyroid stimulating hormone (TSH) does not cross the placenta, while thyrotropin releasing hormone (TRH) requires pharmacologic doses not normally present in the maternal circulation to achieve measurable levels in the fetal circulation.\textsuperscript{2,5,17,21,49,46} Certain other compounds such as long acting thyroid stimulant (LATS), certain rare thyrotoxic hormones, and maternally ingested antithyroid medications do cross the placenta and can induce abnormalities in the newborn.\textsuperscript{5,17,21}

Embryogenesis of the thyroid and pituitary occurs during the first 10 to 12 weeks of gestation.\textsuperscript{4,21,49} By the end of this time, the anatomic migration of the thyroid as well as histologic differentiation has occurred.\textsuperscript{28,41} The capacity to capture iodine and synthesize iodothyronines has also been achieved as evidenced by the presence of measurable amounts of T4 in the fetal serum.\textsuperscript{1,8,10,21,41} The pituitary has similarly completed its histologic differentiation and has begun secreting measurable concentrations of TSH into the peripheral circulation.\textsuperscript{21,24,41}

Hypothalamic maturation is slower, beginning in the fourth and fifth week of gestation and ending in the 30th and 35th week.\textsuperscript{21,41} The TRH is first detectable at about 12 to 14 weeks, the same time the first supraoptic tract fibers and the hypothalamic nuclei can be identified histologically.\textsuperscript{8,21} Maturation then continues into the mid to late third trimester, paralleling the development of the pituitary vascular system.\textsuperscript{21,41}

The third phase, system feedback maturation, appears to begin in the middle of the second trimester. At 18 to 20 weeks gestation, serum levels of TSH begin to show a marked rise, corresponding to the establishment of pituitary vascular continuity.\textsuperscript{4,8,10,21,24,27,41,42,46} This suggests a response to newly available hypothalamic TRH. While the presence of a TRH response has not been clearly proven at this stage in humans, infants of 26 to 28 weeks gestation clearly have fairly normal responses to exogenous TRH.\textsuperscript{8,21,27,41,46}

There is a delay of approximately two weeks after the onset of the rise in TSH before a measurable rise in T4 occurs.\textsuperscript{4,8,10,21,41} Serum levels of T4 steadily increase from 22 to 24 weeks gestation until term.\textsuperscript{30} This increase is most rapid until 28 to 30 weeks when the rate of change in the T4 concentration slows. This change in secretory rate occurs about the same time as the serum TSH begins a decrease which continues until normal values are achieved near term, lasting until very shortly after parturition when there is a marked surge of TSH.\textsuperscript{24,30} By the 35th week of gestation, the entire system appears mature and normal feedback inhibitions and stimulus responses can be demonstrated along the entire axis.\textsuperscript{4,21,41}

Measurable levels of 3,3',5'-triiodothyronines (reverse T3) appear at 18 to 20 weeks, increase to levels well above maternal serum levels by 24 to 26 weeks gestation, and remain stable until parturition when they begin to decrease over several months.\textsuperscript{6,21,41}

### Neonatal Screening Techniques

There are currently several screening algorithms in use in the United States and around the world.\textsuperscript{12,19,21,35,36,38,42} All are based on attempts to avoid false negative results which might represent the surges of TSH and T4 which normally occur a few minutes after birth.\textsuperscript{2,8,17,19,23,30,43} These peak between 12 and 36 hours after birth and return to normal by approximately four days of age. Measurements of T4 and/or TSH are made either in cord blood or in a filter paper specimen taken at discharge from the nursery. The latter is usually drawn at the same time screening for phenylketonuria is performed. A single program, the Northwest Regional Screening Program, has coupled discharge specimens with a routine repeat specimen
obtained at six weeks of age, with a surprisingly high rate of compliance in obtaining both specimens.\textsuperscript{35,36} At present, it is felt that cord blood specimens may be less reliable because of possible artifactual elevations secondary to the stress of delivery or maternal complications. Further, the success rate in obtaining and appropriate handling of these specimens may also be compromised by the sometimes harried state of the delivery room.

Currently, most screening programs use an algorithm similar to that described by Dussault et al, utilizing a base specimen obtained at discharge from the nursery.\textsuperscript{12,19,21,38,42} The T\textsubscript{4} levels are screened first and then TSH values are run on those infants whose T\textsubscript{4} is lower than 2.3 standard deviations (SD) from the daily mean. Those infants with values between 2.3 SD and 2.7 SD below the mean are evaluated on the basis of the TSH values. Infants whose T\textsubscript{4} values are more than 2.7 SD and less than 4 SD below the mean are recalled for serum samples. Those with T\textsubscript{4} values more than 4 SD below the mean are presumed to have primary congenital hypothyroidism. As these programs are currently well established, the cost per T\textsubscript{4} test is quite low as compared to TSH testing. Therefore, this algorithm appears to be more cost effective than TSH screening at present.\textsuperscript{42}

However, it is generally considered that the screening of TSH is somewhat more sensitive in detecting hypothyroid infants.\textsuperscript{21,50} In Northern Europe, several successful screening programs have been established, recalling any infant whose TSH is >20 mIU per ml on the fourth day of life as the basis for further investigation.\textsuperscript{50} This has resulted in an increased number of false positives, and the description of new syndromes involving elevated values of TSH.\textsuperscript{14}

While the results of both types of screening programs show an extremely low rate of false negatives,\textsuperscript{19,14,35} the increasing complexity of the differential diagnosis of thyroid disorders in the newborn suggests that the use of both T\textsubscript{4} and TSH values may be required to detect accurately all infants at risk for thyroid problems.\textsuperscript{41} Both types of programs appear to pick up virtually all infants with primary congenital hypothyroidism. At present, this is the only group for whom the serious long term risk of mental retardation has clearly been demonstrated. Current recommendations of the American Academy of Pediatrics Task Force on Genetic Screening includes recommendations for screening, utilizing both T\textsubscript{4} and TSH, although this is usually taken to be serial rather than concurrent determinations.\textsuperscript{21}

Entities With Abnormal Thyroid Screening Studies

One consequence of the large number of infants currently screened for congenital thyroid disorders has been the description of several newly recognized entities, resulting from errors in the development of the hypothalamic-pituitary thyroid-axis. Several of these appear to be transient with unclear etiologies. Others are fairly subtle but permanent abnormalities. In addition, large numbers of patients have been identified with previously rarely seen anomalies. These data have contributed greatly to our knowledge of the syndromes. In this section, these entities will be examined in groupings according to their respective T\textsubscript{4} and TSH values, as they would present on screening.

Decreased T\textsubscript{4}, Increased TSH

PRIMARY CONGENITAL HYPOTHYROIDISM (Table I)

Primary congenital hypothyroidism is the abnormality the screening programs have been designed to detect. It is the most frequent preventable cause of mental retardation, having an incidence of one in 4000 to 6000 live births.\textsuperscript{12,13,35,36} Current
evidence seems to indicate that there may be a critical period during which treatment must be started in order to prevent the long term mental effects. In humans, this appears to be approximately three months of age. Of those infants treated prior to three months of age, 75 percent achieved IQ's greater than 80 while few of those beginning treatment after this age achieved IQ's in the normal range. However, there is one study by Money et al, which documents a much delayed increase in IQ in a group with delayed diagnosis and treatment. This group showed an average 20 point increase over 25 years with a normal mean IQ of 101, a normal mean value at the end of the study. This might indicate that short term studies may under-estimate the deficit caused by a delay in treatment.

There are two classifications of primary congenital hypothyroidism,—those with thyroid dysgenesis and those with thyroid dyshormonogenesis. Both of these have been thoroughly described elsewhere and will not be discussed in detail here. It is interesting to note that despite inadequate T4 production, the majority of infants with thyroid dysgenesis picked up by the screening program were asymptomatic at birth. Similarly, while a large number of infants with dyshormonogenesis are also asymptomatic at birth, 10 to 15 percent of these infants may have congenital goiter as a presenting clinical finding. While these patients are clinically asymptomatic, bone age films done on a population of patients with athyreosis have shown absence of the distal femoral and proximal tibial epiphyses. These centers are normally present at birth. Hence, despite their apparently normal appearance, these patients do exhibit some features of delayed maturation.

In following the patient with primary congenital hypothyroidism, one should be aware of the fact that TSH does not fall immediately after the institution of appropriate treatment. It may take three to four weeks after adequate serum levels of T4 are produced before TSH returns to normal. It appears that TRH requires adequate reserves of triiodothyronine for suppression rather than circulating T4. Thus, serum T4 is maintained until the reserves are exhausted and a rapid response is seen in TSH to falling serum levels of T4, but only a delayed downward TSH response to treatment. The clinician should not be fooled into increasing an infant's replacement dosage unless adequate T4 has been maintained in the serum for at least four to six weeks.

**TABLE I**

<table>
<thead>
<tr>
<th>Syndromes with Decreased T4, Increased TSH</th>
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<tr>
<td>Primary Congenital Hypothyroidism</td>
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<tr>
<td>Thyroid gland dysgenesis</td>
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<tr>
<td>Thyroid dyshormonogenesis</td>
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<tr>
<td>Transient hypothyroidism</td>
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<tr>
<td>Iodine deficiency</td>
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<tr>
<td>Maternal IgG antibodies to TSH binding</td>
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<tr>
<td>Prematurity</td>
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<td>Maternal Antithyroid Medication</td>
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T4 = Thyroid stimulating hormone
induced similar defects in rat models.\textsuperscript{15} Further, the block in thyroid hormone synthesis created by iodine deficiency would be consistent with the picture of gradual rise of T\textsubscript{4} in the presence of normal TSH found in Belgian infants treated with T\textsubscript{3}.\textsuperscript{11,49} Extensive studies in the infants as well as serial testing done in the infant reported from the Oregon program failed to demonstrate any abnormality which might be helpful in defining the etiology.\textsuperscript{34} All infants seen so far have been treated, at least briefly, because of the inability to differentiate this syndrome from true primary hypothyroidism. With the possibility of a critical period in the first year of life, the risk is too great not to treat these children even if an appropriate marker could be found to aid in differential diagnosis. In all of these cases, the children returned to normal thyroid function by eight to ten months of age and were able to be weaned from therapy at that time.\textsuperscript{11}

A second etiology for transient hypothyroidism has been reported by Matsurra et al.\textsuperscript{37} In this patient, they were able to isolate a specific thyrosuppressive factor which did cross the placenta. This factor appeared to be a series of IgG immunoglobulins that inhibited the binding of TSH. These appeared to block the stimulation of human thyroid adenyl cyclase, thus blocking subsequent increases in cyclic adenosine monophosphate. The antibodies were found in the serum of two siblings at birth and cleared by ten months of age. Similar antibodies were found in the mother, who had Hashimoto’s thyroiditis. Fisher has suggested that these might represent the previously hypothesized thyrosuppressive factors.\textsuperscript{23} Families with apparent familial non-goitrous hypothyroidism have also been reported.\textsuperscript{23} These patients, however, in contrast to those with Hashimoto’s thyroiditis responded well to treatment. This difference suggests that more than one set of placentally transferable thyrosuppressive factors may exist.

Another transplacentally acquired source of transient hypothyroidism is propylthiouracil used to treat maternal Grave’s disease.\textsuperscript{5} Propylthiouracil (PTU) is freely transmitted across the placenta. Thus, it exerts the same antithyroid activity against the fetal thyroid that it does against the maternal thyroid. This can result in a pronounced elevation of TSH as well as congenital goiter from the subsequent glandular hyperplasia. Infants whose mothers have Grave’s disease can also receive long-acting thyroid stimulant (LATS) across the placenta. This substance appears to be a series of immunoglobulins analogous to those recently described in transient hypothyroidism. A small but significant percentage of these infants will be hypothyroid on initial screen and hyperthyroid by the time recall is initiated. This is due to the difference in half-life of PTU (two to three days) and LATS (two to three weeks). Eventually thyroid function does return to normal in all these patients.\textsuperscript{5}

**Prematurity**

The so-called transient hypothyroidism of prematurity probably represents an inappropriate frame of reference rather than improper thyroid function. Infants born at 26 to 32 weeks gestation have T\textsubscript{4} and TSH values outside the “normal range,” as defined for term infants.\textsuperscript{1,4,10,20,22,32,45,51} The laboratory values are correlated with gestational age and increasing birth weight and are inversely correlated with the severity of hyaline membrane disease (HMD).\textsuperscript{1,4,9,10,20,32,45,51} This latter finding is to be expected, since the severity of HMD correlates with general somatic immaturity. Animal studies have shown that there is a marked lag in maturation of the surfactant producing type II alveolar cells in thyroidectomized animals.\textsuperscript{18} Also, in *vitro* studies have shown increased production precursors by cultured alveolar cells in the presence of iodothyronines.\textsuperscript{41}
In addition to generally low levels of T₄, the effect of thyroid hormone in premature infants is further modified by the preferential deiodinization of T₄ to rT₃ rather than the more physiologically active T₃ in the periphery. This may represent a protective mechanism to prevent premature or uneven advancement of certain physiologic processes. Among the protective effects may be the prevention of premature myelinization of the central nervous system prior to appropriate dendritic synaptic development.

As opposed to the other sources of transient hypothyroidism, the vast majority of premature infants has not been treated for this apparent hypothyroidism. Animal studies have indicated potential beneficial effects of treatment on pulmonary maturity if the serum levels of T₃ and T₄ are carefully monitored and controlled. A single reference describes four premature human infants treated with thyroid hormone. These children had symptomatic improvement of apnea, intestinal motility, and weight gain. No data are available regarding their pulmonary or mental development. At present, a cautious approach to treatment seems advisable given the apparently good long term outcome of many premature babies. Further evaluation is needed to document any potential decrease in long term morbidity which might be achieved through administration of thyroid hormone to these children.

**Decreased Total T₄, Normal TSH**

**CONGENITAL THYROID BINDING GLOBULIN DEFICIENCY**

Congenital deficiency of thyroid binding globulin (TBG) was one of the first new entities described by the neonatal screening programs. It remains the most common non-thyroid source of abnormal T₄ results. It occurs in approximately one of every 10,000 to 14,000 live births, and with a male to female ratio of nine to one. While total T₄ is decreased as a sequela of the decrease in protein bound T₄, the levels of free T₄ remain normal. As free T₄ is the most active compound biologically, these infants are clinically euthyroid and have normal values of TSH (table II). An increased T₃ resin-uptake is frequently seen in these children and supports a presumptive diagnosis. However, the specific radioimmunoassay for TBG is available in most reference laboratories and should be utilized to confirm TBG deficiency.

Multiple reports of familial TBG deficiency have indicated X-linked inheritance in most cases, although autosomal dominant inheritance occurs in some families. Heterozygotes have only half the normal serum values for TBG, but this usually is enough to bring the total T₄ into the normal range. Thus heterozygotes are rarely detected on routine thyroid studies. A deficiency in the hepatic production of TBG appears to be the pathophysiologic mechanism of gene expression in this case.

As the hepatic production TBG appears to mature fairly early, normal production of TBG is achieved even in very premature infants. Thus, all infants with decreased values of TBG can be assumed to carry the gene for TBG deficiency. As free T₄ remains normal, these children require no treatment.

**TRH DEFICIENCY AND HYPOPITUITARISM**

The multiple syndromes which involve anomalies of the hypothalamic-pituitary

| Table II |
|-----------------|-----------------|-----------------|
| **Syndromes with Decreased T₄, Normal TSH** | **Congenital TBG Deficiency** | **Decreased Secretion of Thyrotropin Releasing Factor** |
| | | **Hypopituitarism** |
| | | **Transient Hypothyroxinemia** |

TSH = Thyroid stimulating hormone
TBG = Thyroid binding globulin
axis are extremely rare, representing a total incidence of approximately one in 100,000 live births. Infants with isolated deficiency in TRH synthesis represent the largest of these groups. They should be suspected in infants with a low T₄, low T₃, and low free T₄ values in the presence of a normal value of TSH. In these patients, a TRH stimulation test utilizing exogenous TRH and measuring TSH response will identify whether the defect is the level of the pituitary (secondary hypothyroidism) or the hypothalmus (tertiary hypothyroidism).

Infants with multiple pituitary trophic hormone defects may first present with abnormal values on the neonatal thyroid screen. These children may also have a history of neonatal hypoglycemia. This combination dictates a rapid investigation as children with true panhypopituitarism will also require adrenal supplementation. Failure to provide this may be life threatening. These children, as well as those with other forms of secondary and tertiary hypothyroidism, require the usual thyroid replacement therapy. Their management requires close clinical evaluation of the adequacy of dose, as TSH cannot be utilized to gauge the adequacy of replacement.

TRANSIENT HYPOTHYROXINEMIA

The term “transient hypothyroxinemia” has been used to describe the phase during the post-natal maturation of premature infants, where the TSH has begun to fall and the total T₄ has not yet risen to “normal” levels. This occurs most frequently in otherwise healthy infants of 28 to 30 weeks gestation. It may effect up to 25 percent of all infants of less than 35 to 37 weeks gestation. Infants with hyaline membrane disease or other difficulties tend to have more consistently elevated values of TSH as discussed previously. The normal longitudinal development in these children indicates that hypothalamic maturity is lacking in these children. This can be confirmed by the fact these children have normal TSH responses to exogenous TRH. As with the “transient hypothyroidism” described in premature infants, the term “transient hypothyroxinemia” seems to represent an inappropriate frame of reference for describing this normal developmental phenomenon.

Elevated TSH With Normal T₄ (Table III)

A number of syndromes can present with the sole finding of elevated levels of TSH. Many of these are either mild variants of processes that can result in true hypothyroidism or may, in some cases such as ectopic thyroid, represent a process that has not yet progressed far enough for the serum levels of T₄ to be effected. There remains a large number of cases of increased TSH for which there is no explanation. Some of these cases have proven transitory. Virtually all of these situations had gone undetected in the neonatal period prior to the initiation of large scale screening programs.

TRANSIENT HYPERTHYROTROPENEMIA

The majority of infants with transient elevations of TSH (transient hyperthyrotropenemia) have been reported in Europe. No incidence figures have been given. Regions with endemic goiter seem to have the highest percentage of these patients. As noted earlier, low iodine diet may account for these transient anomalies which seem to improve rapidly.

TABLE III

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<thead>
<tr>
<th>Syndromes with Normal T₄, Increased TSH</th>
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<tr>
<td>Transient Hyperthyrotropinemia</td>
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<tr>
<td>Iodine Deficient</td>
</tr>
<tr>
<td>Idiopathic</td>
</tr>
<tr>
<td>Maternal Drugs</td>
</tr>
<tr>
<td>Cross Reactive Proteins (Artifactual Elevations)</td>
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<tr>
<td>Ectopic Thyroid Gland</td>
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TSH = Thyroid stimulating hormone
when the infant is started on a formula with adequate iodine. Teller and co-workers in Ulm have followed serial TSH measurements in the first day of life and have shown that the course of TSH elevation parallels that of normal newborns.\textsuperscript{49} Whereas TSH returns to normal in 48 to 96 hours for most newborns, in these children it may take two to three times as long.

Engberg et al from Sweden have reported a series of 44 infants with transient hyperthyrotropenemia.\textsuperscript{16} They report an incidence in their population of one in 140 live births. This is a much higher figure than reported anywhere else. Almost one-half of these children were delivered by Cesarean section. No clear explanation exists either for the increased incidence in this population or for the high percentage of children with Cesarean deliveries.

Pure elevations of TSH have also been reported from Japan where the incidence appears to be one in 19,000 live births.\textsuperscript{37,39} As with other studies, all measurements of T3, T4, free T4, and TBG have been normal. By utilizing "paired TSH assay methods," artifact free results have been virtually certain. In the seven patients reported, all had normal TSH values by seven to nine months of age. No treatment was initiated in any of these cases. All children were clinically euthyroid. One of the present authors (BEW) has had experience with two similar cases. Both children presented with low normal T4 values on a neonatal screen. The TSH elevation was present which initiated recall of these patients for further follow-up. Serum values on both infants at three to four weeks of age revealed normal T4 and persistence of the moderate TSH elevation. Subsequently, TBG was shown to be normal, suggesting normal levels of free T4. Serum T3 resin-uptake values were also normal. It was opted to place these patients on partial replacement therapy. Subsequent dose titrations showed that both patients required only 1/8th to 1/4th grain per day of desiccated thyroid (utilized because of logistic problems obtaining appropriate dosage forms of sodium levothyroxine) to suppress TSH. Both infants were successfully weaned from supplemental thyroid by nine months of age and have shown no further abnormalities of thyroid testing.

The mechanism of TSH elevation remains undefined. Proposed mechanisms have included reduced thyroid responsiveness to TSH or inefficient hormone production at the thyroid level.\textsuperscript{39} Delayed maturation of the iodothyroine-hypothalamic feedback system has been suggested but thought less likely as it would usually result in increased thyroid hormone levels. However, the mechanisms of individual homeostasis are not well understood. The ease with which these patients were suppressed with only minimal amounts of exogenous replacement would suggest a defect in feedback inhibition.

**Maternal Drugs**

In some cases of maternal hypothyroidism treated with PTU, insufficient quantities of the drug will cross the placenta. Thus, total suppression of the fetal thyroid is not achieved. The fetal thyroid remains capable of secretion of normal amounts of T4 but only under increased stimulation by elevated TSH. As mentioned earlier, the half life of PTU is relatively short.\textsuperscript{5} Thus, the entire hypothalamic-pituitary-thyroid axis is usually demonstrably normal within a few weeks after birth.\textsuperscript{5}

**Cross Reactive Proteins**

Gendrel and co-workers have reported a series of seven infants who presented on neonatal screening with elevated TSH and normal T4 and T3.\textsuperscript{25} These infants all had normal physical examinations, thyroid scintigraphy, and negative antibody determinations. When parallel serial dilutions were performed with and without the addition of normal rabbit serum (NRS), those tubes with NRS showed nor-
mal TSH response. Rabbit serum was the chosen additive because the anti-TSH sera used in the test were obtained from rabbit sources. Further history revealed that all seven mothers of the affected infants had received vaccinations from cultures grown on a rabbit lung homogenate base six months to four years before conception. Previous non-specific cross-reactivity has been shown in euthyroid subjects when anti-serum to porcine TSH has been utilized. Chromatographically, these heterophilic antibodies have been shown to be indistinguishable from IgG. Hence, transplacental acquisition is possible and, as would be expected, all infants had normal TSH values by standard radioimmunoassay values by six months of age. This further supports the maternal etiology of these cross-reactive proteins.

Ectopic Thyroid

A variant of thyroid dysgenesis, ectopic thyroid glands are frequently capable of producing normal amounts of thyroid hormone at birth. This capability extends for varying amounts of time into extra-uterine life. In one study, ectopic thyroid glands accounted for 24 percent of cases with primary non-goiterous hypothyroidism. Of these, one-half became hypothyroid within the first two years of life, although they had not been picked up within the neonatal period. As the ectopic gland becomes unable to respond to the increasing needs of the body in extra-uterine life, the TSH values are the first to become abnormal. The gland is able to produce adequate T₄ under this increased stimulation before lapsing into true thyroid failure. It has been hypothesized that anatomic maldescent of the gland may be secondary to maldevelopment, as these glands are almost always hypoplastic. This hypoplasia contributes to their eventual inability to produce adequate thyroxine. There appears to be a familial incidence of ectopy, but no clear genetic mechanism has been characterized.

Further Investigation and Treatment

While the algorithm of Dussault et al can be utilized to evaluate the majority of cases, there are a number of entities which it cannot precisely designate. In infants with low T₄ and elevated TSH values, a detailed history should reveal etiologic sources, such as maternal antithyroid medications or prematurity, which can be expected to have transient effects only on thyroid function. Demographic data may suggest iodine deficiency in the maternal diet as an etiology for abnormal results. At the present time, replacement thyroid therapy does not seem indicated in these cases, although its possible role in modifying the morbidity in sick prematurity infants remains under investigation.

The possibility of hypopituitarism with life threatening adrenocortical insufficiency warrants rapid investigation in the infant with demonstrably low T₄ and normal TSH values. A stimulation test with thyrotropin releasing factor will rapidly rule out hypothalamic problems from among these cases. Infants with elevated TSH should receive radionucleide scans to look for ectopic thyroid glands. These children clearly need close follow-up with replacement therapy at the first signs of incipient hypothyroidism. Infants with normal anatomy and no indication of maternal drugs or iodine deficiency raise a major question in terms of therapy. At present, the majority of these patients have been without therapy, and no morbidity has been noted. The ease with which these patients may achieve TSH suppression and the lack of long term data would perhaps suggest a cautious approach with replacement. The severe developmental consequences, if treatment is not initiated early, represent the major argument for replacement therapy. Further studies may clarify this situation.

References


35. LA FRANCHI, S., MURPHY, W. H., BUIST, N. R. M., LARSEN, P. R., and FOLEY, T. P.: Neonatal


