GRAND ROUNDS IN PEDIATRIC ENDOCRINOLOGY

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CASE PRESENTATION

A 10-week old child was brought to the clinic because of abdominal distention. She was born to a single retarded mother following normal pregnancy, labor, and delivery at term. In the clinic she was found to have cyanosis and weak pulses and was admitted to the hospital for a cardiac workup. Further examination in the hospital noted a hoarse cry, a large tongue, noisy respiration, pallor and mottling of the skin, cold hands and feet, persistent lanugo hair, a large open fontanelle, and an umbilical hernia. The scleras appeared jaundiced. Reflexes were characterized by brisk jerk but very slow return. Facial appearance was that of a newborn. Soft tissues felt doughy. Her weight was close to her birthweight and mother could not recall when was the last time she had a bowel movement. She was being formula fed but was a "poor feeder", taking very little and slowly. She was a "good baby", never crying or fussing. X-ray film of the ankles showed a prenatal bone age (absence of the distal femoral epiphysis.

Figure 1- 10-week-old child demonstrating features described above.

QUESTIONS

1. The findings described in this patient can only be explained by congenital hypothyroidism, as listed in the discussion below.
2. Laboratory studies of the patient in Figure 1 confirmed a very low thyroxine value with a high thyroid stimulating hormone (TSH) concentration. When should hypothyroidism be suspected in a neonate?
   A. If the infant is premature or small for gestational age.
   B. If the baby is not having normal bowel movements.
   C. If the baby is feeding poorly.
   D. If the baby does not cry or fuss.
   E. All of the above.
   F. B, C, and D.
3. The child in Figure 1 was started on 37.5 mcg of levothyroxin daily. Over the subsequent 24 hours she had a substantial diuresis and had her 1st spontaneous bowel movement. She began feeding vigorously and crying when she was hungry, gaining weight rapidly and decompressing her abdomen with regular bowel movements. When should hypothyroidism be treated?
   A. As soon as it is suspected and a blood sample drawn.
   B. When the diagnosis is confirmed by laboratory testing.
   C. When x-ray studies reveal markedly delayed maturation.
4. The low hemoglobin level in congenital hypothyroidism requires iron supplementation for correction.
   A. True
   B. False
5. In adults, severe hypothyroidism must be treated very slowly to prevent heart failure. This is also true in children.
   A. True
   B. False
6. It is necessary to know whether hypothyroidism is due to absence of the thyroid gland, faulty migration

of the embryonic gland, or an inborn error of metabolism in order to properly treat the condition.
A. True
B. False

7. With thyroid hormone treatment of congenital hypothyroidism, hair loss may be rapid and extensive. The proper response to this is to:
A. Reduce the dosage, and raise it back slowly.
B. Reduce the dosage and recheck thyroid hormone level
C. Maintain the same dosage.

8. If congenital hypothyroidism is due to iodine deficiency,
A. A goiter is present.
B. Thyroid hormone values will be normal
C. Treatment can be with iodine supplementation
D. Treatment should be with thyroid hormone.
E. A & C.
F. A & D.

9. Desiccated thyroid is preferable to levothyroxin for replacement therapy because it is a natural product.
A. True
B. False

10. Pharmacists can put thyroid hormone into suspension for easier administration to babies.
A. True
B. False

11. How long is it absolutely necessary to continue treatment in congenital hypothyroidism?
A. Until brain growth has reached the point where mental retardation will not occur due to thyroid deficiency (age 3 years).
B. For life.
C. Until completion of adolescent growth and development.
D. Depends on the cause of the hypothyroidism.

12. The spectrum of congenital hypothyroidism due to maternal iodine deficiency includes:
A. Spastic quadriplegia
B. Deafness
C. Mental retardation
D. Atrophy of the thyroid gland
E. All of the above
F. A, B, & C.

13. The most sensitive test of thyroid deficiency and the most useful for monitoring treatment is:
A. Urinary iodine
B. Serum total thyroxine
C. Serum free thyroxine
D. Serum TSH.

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DISCUSSION

Congenital hypothyroidism may be due to an anatomic defect in the thyroid gland, an inborn error of thyroid production, or iodine deficiency. Anatomic defects include athyreosis (absence of formation of the thyroid gland) or an ectopic gland due to failure of normal migration of the thyroid gland from the base of the tongue to the neck with inadequate formation (usually with a milder hypothyroidism). In ~10% of cases in iodine sufficient countries, there is an inborn error of thyroid hormone synthesis. The term "endemic cretinism" has been used to describe geographical clusters of infants with hypothyroidism in areas with iodine deficiency. Iodine deficiency has been abolished in most such areas by mandatory iodination of salt, but this remains a common problem in some areas of Africa, Asia, and South America. "Sporadic cretinism" refers to congenital hypothyroidism that occurs in all geographic areas unrelated to iodine nutriture.

Thyroid hormone is unique for its essential role in central nervous system development, affecting branching of neurons. Thyroid hormone deficiency in infancy results in irretrievable losses of intellect, depending on duration and severity, unless detected and treated very early. With an incidence of approximately 1/4000 newborns in Western countries, this is a preventable cause of mental retardation that has been successfully addressed by newborn screening and treatment within the 1st 3 weeks of life in all developed countries. The prevalence in black infants is about a third that of white infants in non-iodine deficient settings. Iodine deficiency remains the most common cause of preventable mental retardation. In endemic areas, frequency of congenital hypothyroidism may be as high as 1/500. In addition to its critical function in brain development, thyroid hormone is also the only hormone deficiency that results in total growth failure (Figure 2).

The clinical features of hypothyroidism in infancy can be classified into 3 groups of manifestations, those due to hypometabolism, myxedema, and maturational delay.

1. Hypometabolism
-cool skin
-low hemoglobin (appropriate for low oxygen carrying requirement)
-weak cry
-poor feeding
-hypoactivity
-vascular stasis

-cardiac hypoactivity/bradycardia
-constipation
-dry skin
-hypercholesterolemia

2. Myxedema
-pseudo-hypertrophy of muscles
-doughy tissues
-hoarse cry
-big tongue
-thick skin
-rapid weight loss with treatment

3. Maturational delay
-growth failure
-mental retardation
-placid temperament "good baby"
-carotenemia
-drug intolerance
-coarse immature facies with depressed nasal bridge (Figure 3)
-persistent neonatal jaundice
-persistent lanugo hair
-umbilical hernia
-delayed dental development and enamel hypoplasia
-retarded bone age and epiphyseal dysgenesis
-open fontanelles

Figure 2- A four-year-old with sporadic congenital hypothyroidism showing classic signs, including neonatal body proportions and size, and inability to stand without support, with a normal child of the same age.

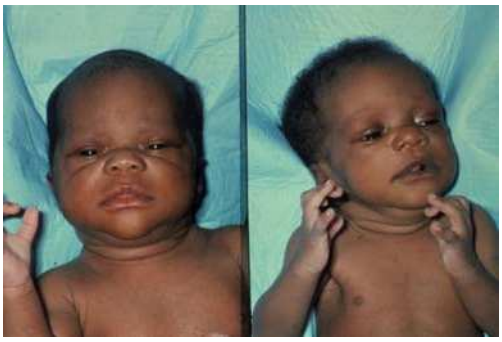

Figure 3- Two-week-old twins, one of whom, on the left, detected as hypothyroid on neonatal screening and found to have absent thyroid gland. Note puffiness of face, depressed nasal bridge, large tongue, and less alert appearance compared to normal twin.

GRAND ROUND ANSWERS

2. F. Congenital hypothyroidism does not affect growth in utero. However, severe iodine deficiency during pregnancy can increase the risk for stillbirth, abortion, and congenital anomalies.
3. A. If the diagnosis is in error, there is absolutely no harm from administering thyroid hormone to a child who does not have thyroid deficiency, and if the child improves, laboratory studies showing normal thyroid function should be questioned and treatment continued until age 3, when it can safely be stopped for a month to re-test serum TSH. The loss of brain development is directly related to the duration of thyroid deficiency in the first couple of years of life.
4. False. The low hemoglobin level is the result of the low demand for oxygen carrying capacity in the hypothyroid infant, and this is reflected in the fact that this is a normochromic, normocytic anemia. Unless there is true iron deficiency, iron stores and normal intake will result in correction as oxygen carrying capacity requirement increases with thyroid replacement.
5. False. Long-term hypothyroidism in adults results in myocardial insufficiency which is further compromised by the mobilization of myxedema fluid from the subcutaneous tissues. However, in severe congenital hypothyroidism of long standing (years) in children, hyperthermia may develop with full dose replacement therapy, dictating a more gradual intervention. In such children, the urgency for rapid restoration of neuronal development is, unfortunately, long past.
6. False. All hypothyroid conditions are treated with full dose replacement therapy. However, it is occasionally helpful to show the parents that there is no thyroid gland or that it is a tiny remnant in the wrong place to assure compliance with therapy. In this case radioactive technetium scanning is the best approach and should be done immediately, before treatment, but should not result in a delay in treatment. Once the child is treated, the TSH attempt to stimulate a thyroid remnant diminishes and the test may be inaccurate.
7. C. It is very important to warn parents that there will be massive hair loss which is simply the loss of baby hair that has been arrested since birth and that this is a good thing so that more mature hair can grow in. Parents have occasionally stopped medication thinking that this is a toxic effect.
8. F. There are 2 distinct types of congenital hypothyroidism resulting from maternal iodine deficiency, but these may also exist in a mixed form. The more common of these is neurologic cretinism, characterized by spastic quadriplegia and deafness. The myxedematous form is the one most frequently seen in central Africa, with severe hypothyroidism, and thyroid atrophy and fibrosis. Therefore, the thyroid gland may not be capable of adequately processing iodine, making thyroid replacement therapy the more rational approach.
9. False. While desiccated thyroid may have to be used in some places where it is the only form available, it is not recommended for a number of reasons. Levothyroxin is safe, effective, inexpensive, easily administered, and readily monitored in the laboratory. Desiccated thyroid is made from pooled animal tissue with unknown potential risks from viral or prion contamination and uncertain, inconsistent biological potency.
10. False. It is very difficult to keep levothyroxin in suspension with inconsistent drug delivery. Parents can crush the pills in a spoon and administer with a small amount of breast milk, water, or juice and give it to the child with a syringe or eyedropper. They should not crush the pills and put them into the infant's bottle, as the thyroid particles will cling to the side of the bottle and not get to the baby. The dosages of levothyroxin are:
    -<6 months: 6-8 mcg/kg/day or 37.5-50 mcg minimum dose
    - 6-12 months: 6-8 mcg/kg/day or 50-75 mcg
    -1-5 years: 5-6 mcg/kg/day or 75-100 mcg
    - 6-12 years: 4-5 mcg/kg/day or 100-150 mcg
    ->12 years: 2-3 mcg/kg/day or 150 mcg
11. A. As noted above, if diagnosis is in doubt, treatment can be stopped at age 3 and resumed if the thyroid function studies are abnormal after one month. If confirmed, treatment must be continued for life.
12. E. (See #7 above)
13. D. Elevated TSH is the most sensitive indicator of hypothyroidism, except for that due to hypopituitarism, which is very rare and not associated with deficit in neurologic development. Some infant screening programs use TSH as the primary screening test. TSH is controlled by a feedback mechanism; triiodothyronine (T3), the active form of thyroid hormone is the feedback suppressor of TSH. If deficient circulating thyroxine for conversion to T3, mostly in the peripheral tissues, TSH attempts to push the thyroid gland to make more thyroxine (T4) to be converted to T3. This is what causes enlargement of the thyroid gland when the gland is present but unable to synthesize T4 because of an inborn error, as in approximately 10% of congenital hypothyroidism, or because of iodine deficiency.