

DELAYED DIAGNOSIS IN CONGENITAL HYPOTHYROIDISM: CASE SERIES.

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Congenital hypothyroidism (CH) may present normal at birth and, therefore, may evade diagnosis in the neonatal period. When it is diagnosed and treated early, its most important complication, mental retardation, is preventable. The signs of congenital hypothyroidism are nonspecific in neonates and hence diagnosis can be delayed or missed entirely. Only 5%-10% of cases have characteristic clinical findings to aid in diagnosis at birth so early diagnosis and treatment in countries where neonatal screening (NS) is not done is almost uncertain. However, as the child grows clinical features become more conspicuous. If diagnosed and treated within the first week of life intelligence and developmental milestones are comparable to normal siblings and peers. Ghana and many other resource constrained countries do not have systematic NS programs for congenital hypothyroidism so it is more likely that children born with congenital hypothyroidism are missed on diagnosis. Such babies are likely to have gross developmental delay, severe mental retardation and short stature and may not come to timely medical attention. Doctors and other health professionals who attend to children should have high level of suspicion and screen babies with the least clinical suspicion or refer them to centers where they can be investigated and managed. Biochemical diagnosis, thyroid stimulating hormone (TSH) assay, is readily available and the treatment, L-thyroxine, is also available and affordable in Ghana.

Key words: Congenital hypothyroidism, mental retardation, neonates.

INTRODUCTION

Congenital hypothyroidism (CH) is a common cause of severe mental and physical retardation when treatment is delayed, missed or suboptimal dose of L-thyroxine is given. The clinical features of hypothyroidism are nonspecific in the neonatal period, and typical clinical features are observed in only 5-10% of the neonatal cases. (Adeniran and Limbe, 2012; Kurtoglu et al., 2009) Therefore, diagnosis is often delayed or missed entirely with consequent development of complications such as severe growth restriction, delay in developmental milestones and profound mental retardation. (Adesanmi et al., 2009; Rastogi and LaFranchi, 2010) However, beyond the neonatal period signs and symptoms of congenital hypothyroidism become more prominent and clinical suspicion should be easier. (Maswiryati and Westra, 2003; Rastogi and LaFranchi, 2010) A report is made of two babies with CH whose diagnoses delayed despite presentation with prominent features of CH to hospitals in Ghana.

CASE PRESENTATION

Case # 1

A 9 month old female baby (Figure 1) was referred to Pediatric Endocrine Clinic (PEC), Komfo Anokye Teaching Hospital (KATH) with a diagnosis of failure to thrive on the 24th September, 2015. She presented to a district hospital with poor feeding at age 1 month, which was progressive and worsening. Mother had to express breast milk for her because she could not suck. Pregnancy was uneventful. Mother had a healthy pregnancy and delivered at 42 weeks via spontaneous vaginal delivery in a hospital with birth weight 4.0 kg. She passed meconium on the second day of life and thereafter she passed stools once every 2 weeks. Mother reported the bowel habit to a hospital and a doctor assured her that it was normal. She could sleep throughout the day. She developed neck control at 6 months of age but could neither sit nor crawl when she was seen at age 9 months. The parents are married, monogamous, non-consanguineous. This is the



Figure I (photograph of Patient at 9 months old)

only child of the couple. Mother is 27 years and father is 36 years. On examination, weight was 5.2kg, length 61cm and head circumference 40.2 cm (all below the 3rd percentile on WHO growth chart). She had dry skin, protruding tongue, mild periorbital edema, cold extremities but axillary temperature was 36.1°C. Anterior fontanelle was widely open, 6 cm x 5 cm, but posterior fontanelle was closed. No goiter. Respiration was 30/minute, heart rate was 100 beats/minute, regular. She had umbilical hernia of 6 cm in diameter. She was conscious but hypotonic with weak reflexes.

Investigations

Hemoglobin= 9.9 g/dl, WBC= $21.7 \times 10^9/L$ with 69.4% polymorphs and 30% lymphocytes.

Thyroid profile

TSH= 176.6 uIU/ml (0.3-7.0) and a total T4= 0.9 µg/dl (4.4-12.0).

Case #2

A 2 year old female (Figure II) was referred to PEC, KATH as a case of Down Syndrome with failure to thrive. Mother realized that baby was feeding poorly and could sleep for almost the whole day after one month of age. She reported to a hospital and the baby was diagnosed as malnutrition and was prescribed vitamin preparations for 8 months. Mother self referred to another hospital where the attending doctor diagnosed rickets and treated with calcium and vitamin D syrup for more than 1 year before the baby was referred to PEC, KATH. Mother was 32 years and father 39 years, they are married, non consanguineous.

On examination, weight was 6.2 kg, height was 60 cm and head circumference 40.8 cm (all below 3rd percentile on WHO growth chart). She had dry skin, very big protruding tongue, axillary temperature was 36.1°C. Anterior fontanelle was open, 2 cm x 2 cm.

Respiration was 36/minute, heart rate was 98 beats/minutes, regular. She had umbilical hernia of 8 by 6 cm in diameter. She was hypotonic with weak reflexes.



Figure II

Thyroid profile

TSH= 200.6 uIU/ml (0.3-7.0) and a total T4= 0.2µg/dl (4.4-12.0).

TREATMENT

Treatment should start as soon as diagnosis is confirmed. Early diagnosis and treatment are crucial to prevent mental retardation in affected babies. There is inverse relationship between age at the start of treatment and intelligence quotient, the worst outcome being observed in infants diagnosed after the age of 6 months.(Hassan et al., 2003; Léger et al., 2014)Both patients being diagnosed at 9 months and 2 years of age respectively would incur some neurocognitive impairment. However, they will be adequately treated and followed up to ensure that they obtain as maximum neurocognitive function as possible.

The goal of therapy is early and adequate thyroid hormone replacement to normalize the TSH concentrations. An initial dose of L-thyroxine at 10-15 mcg/kg/day is recommended to quickly normalize TSH.(Léger et al., 2009) L-thyroxine tablet is crushed on a spoon and mixed with about 5 mls of water or breast milk and given in the morning at the beginning of feed although it can be given anytime of the day. TSH, in special situations, T4 (or FT4) should be monitored at regular intervals.

Outcome and follow-up

There has been significant improvement following thyroxine replacement therapy (TRP). One month after treatment Case # 1 could sit without support (Figure III) and three months after treatment she started crawling. She could stand with support (Figure IV) after 9 months of treatment and could walk independently after 12 months of TRP. Similarly, one month after TRP, Case #2 gained neck control (Figure V) and after four months of treatment she could sit without support (Figure VI).



Figure III(Photograph of Patient 9 months after treatment)



Figure IV (Photograph of patient at 12 months after treatment)



Figure V



Figure VI

DISCUSSION

Most infants with CH are asymptomatic at birth even if there is complete agenesis of the thyroid gland due to transplacental transfer of thyroxine during fetal life.(Léger et al., 2014; Vulsma et al., 1989)The causes of CH include developmental defect of the thyroid gland referred to as thyroid dysgenesis, a defect in one of the steps involved in the biosynthesis of thyroid hormone. Iodine deficiency is a common cause of CH and it still affects several millions of infants worldwide.(Zimmermann, M. B., 2009)About 10% of children born in area of severe iodine deficiency are at risk of developing hypothyroidism.(Buxton and Baguune, 2012; Zimmermann, M. B., 2009)In rare cases CH may be due to defect in the pituitary or hypothalamus.

Clinical features of CH include slightly increased head size due to myxedema of the brain, prolongation of physiological jaundice, large tongue, nasal obstruction, coarse cry, prolong sleep and hypotonia. They may have umbilical hernia (Figures I and IV), hypothermia, constipation, edema of genitals and extremities, cardiomegaly, bradycardia and asymptomatic pericardial effusion.(Léger et al., 2014; Maciel et al., 2013) Symptoms appear gradually and can be very subtle in the neonatal period and so if NS is not done, the diagnosis is often delayed or can totally be missed.(American Academy of Pediatrics et al., 2006) If a child with congenital hypothyroidism is not diagnosed at birth and managed, severe complications can result. These include developmental delay, skeletal growth delay and severe mental retardation.(Hassan et al., 2003; Léger et al., 2014; Rastogi and LaFranchi, 2010) Although, some of these clinical features were present in these patients, even from birth, and more signs became prominent as they grew beyond the neonatal period, the doctors and other health workers who attended to them did not recognize these significant signs and hence the delay in diagnosis and treatment. Treatment of CH should be initiated as soon as diagnosis is confirmed. Total thyroxine (TT₄) or Free thyroxine(FT₄) concentration should be maintained in the upper half of the age-specific reference range. They were each reviewed 2 weeks after the starting TRP and thereafter every 1 to 3 months until the age of 12 months.(Léger et al., 2014)

NS programs are extremely successful in diagnosing affected babies so that they can be appropriately managed. If

babies with congenital hypothyroidism are diagnosed at birth and adequate TRP is done, development and intelligent quotient are comparable to normal cohort or normal siblings.(Adeniran and Limbe., 2012; Adesanmi et al., 2009; American Academy of Pediatrics et al., 2006) Unfortunately, Ghana and many developing countries do not do NS for CH and so the only means of diagnosing affected babies is high level of suspicion and doing sporadic and isolated screening.

Once clinically suspected, TSH is done as a screening test and if it is high, the diagnosis is confirmed by doing the serum free T4 and TSH levels. The TSH will be elevated (>10 mcU/ml) and free T4 will be low (<6.5 mcg/dl) in neonatal period in patients with CH. Intrauterine deprivation of thyroid hormone may retard osseous centers and manifest as absent distal femoral epiphysis at birth.(Léger et al., 2014; Vulsma et al., 1989) Babies diagnosed months after birth present with delayed bone age. Etiological diagnosis of congenital hypothyroidism, such as technetium-99 nuclear scanning, ultrasonography, Thyroxine Binding Albumin assay, is important for establishing permanence and determining the risk of recurrence in a family.(Léger et al., 2014) Ultrasonography of the thyroid gland can be used to assess the size and the location of the gland. It can be useful in skillful hands. These investigations should not determine or delay TRP in a baby with confirmed diagnosis.(Léger et al., 2014) It is likely that many babies with CH in Ghana are misdiagnosed as it mimics many other disorders and newborn screening is not done. The facial features, flat nasal bridge, macroglossia, umbilical hernia, and hypotonia may suggest Down syndrome or a metabolic storage disease. Prolonged jaundice and a protuberant abdomen may suggest a congenital liver disorder such as biliary atresia. Rickets may be misdiagnosed for CH because of poor growth and hypotonia. Because babies with congenital hypothyroidism fail to thrive as a result of poor metabolism and poor feeding they may be misdiagnosed as malnutrition. Both patients were misdiagnosed and managed for acute severe malnutrition, while case #2 was further misdiagnosed and mismanaged as rickets and Down Syndrome. However, they presented with prominent and specific features of CH including poor feeding, constipation, protruding tongues, umbilical hernia, excessive sleep and delayed developmental mile stones.

It is likely a lot of babies with CH are being missed on diagnosis as from clinical features only 5-10% of babies with congenital hypothyroidism are diagnosed in the neonatal period.(Rastogi and LaFranchi, 2010) The only way out for pediatricians in Ghana and other developing countries where NS is not done is to increase their level of suspicion and screen any baby with even subtle clinical features. Biochemical diagnosis can easily be done in many parts of Ghana and L-thyroxine is readily available. The Ministry of Health and Ghana Health Service should consider NS for CH for the whole nation, keeping in mind that iodine deficiency needs prior correction.(Buxton and Baguune, 2012)

DECLARATION OF INTEREST

No conflict of interest.

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