Introduction

Congenital hypothyroidism (CH) is the commonest cause of preventable developmental delay with an incidence of 1/3500-4500 newborns. The incidence of symptomatic cases has decreased dramatically in the developed countries with the advent of newborn screening. However, much work still needs to be done in the developing world in improving awareness and devising newborn screening strategies etc. In this article, we discuss the diagnosis and management of congenital hypothyroidism.

Diagnosis

With the worldwide implementation of newborn screening (with the exception of some developing countries), majority of cases of CH are diagnosed following abnormal newborn screening. Most countries measure Thyroid stimulating hormone (TSH) as the primary test, with the test being done beyond 48 hours after birth to avoid false positives from the postnatal TSH surge. False negative screening result may be seen in preterm babies, central hypothyroidism and hypothyroxinaemia. It is unlikely that missing central hypothyroidism by this method is a significant problem, as most such babies are diagnosed early due to manifestations of other anterior pituitary hormone deficiencies.

Confirmation of Diagnosis

Immediate endocrine evaluation is required on obtaining an abnormal screening result. History of maternal drugs, medications, maternal hypothyroidism and family history should be elicited.
Tests include repeat TSH, free T4 (fT4) and T3. Combination of low fT4, low normal T3 and elevated TSH confirm diagnosis of primary CH [2]. Treatment should be initiated as soon as possible and no later than 2 weeks of age, preferably immediately after confirmatory venous TFT [4].

**Investigations**

Though clinical practice is variable in terms of which investigations are carried out after diagnosis of CH, it is recommended to carry out ultrasound and radio-isotope scanning in all cases early. This will help in understanding the underlying cause, reinforcing to the parents the potentially lifelong treatment needed as well as removing the need for possible re-evaluation at 2-3 years in most cases.

**Ultrasonography (US)**

US can detect thyroid tissue not identified on thyroid scintigraphy (TS) and also pick up morphological thyroid abnormalities. Absent gland is seen in agenesis and small ectopic nubbin in dysgenesis. In maternal thyroid receptor blocking antibody (TRB-Ab) and DHG, the gland is normal and goitrous respectively [5,6].

**Thyroid Scintigraphy (TS)**

TS is the gold standard in evaluating CH especially ectopia and also helps diagnose agenesis. Iodine-123 or technetium pertechnetate are used of which the former is preferred. As TSH suppression decreases uptake, it should be carried out within 3-5 days of start of treatment (with TSH >5 mU/l) [5]. Absent radioactive iodine uptake (RAIU) indicates aplasia or hypoplasia but if US is normal, may indicate TSH-receptor defect, iodine-transport defect (N/I symporter (NIS)) and maternal antibody TRB-Ab [2]. Uptake in a normal or goitrous gland is suggestive of DHG. Scintigraphy may not be considered essential by some as it may not change the treatment indication and the dose and treatment should not be delayed to perform scintigraphy [5,6].

Once the above two tests have been carried out, the diagnosis can be narrowed down to dysgenesis (in which case no further testing is needed) and DHG, in which case both genetic and enzyme pathway based tests may be needed. Other tests in such cases include Perchlorate discharge test (PDT), Thyroglobulin (Tg), Serum TRB-Ab, genetic screening, urinary iodine and Thyrotrophin releasing hormone (TRH) testing depending on history and specific evaluation. Major congenital especially cardiovascular anomalies are reported to occur in up to 10% of newborns with CH [9]. All patients require hearing screen (hearing impairment seen in 20%) and cardiac evaluation [7,8]. X-rays of the knee for bone age to assess severity was previously done as it indicates antenatal hypothyroidism. In central hypothyroidism, assessment for other hormone deficiencies, MRI brain, and ophthalmology evaluation are required. TSH beta mutation should be checked in isolated TSH deficiency [9,10,11].

**Management**

**Levothyroxine (L-T4)**

After confirmation of diagnosis, immediate treatment with L-T4 10-15 µg/kg normalizes T4 and TSH within 7-30 days [9]. Lower doses were found not to normalize TFT. Higher dosing (12-17 µg/kg/d) normalizes fT4 in 3 days and the TSH in 2-4 weeks with full scale IQ scores 11points higher than those started on 10-15 µg/kg/day but at risk of side effects [12,13]. Initial dose of 50 µg daily (14 µg/kg/day) is recommended for 5 to 7 days with subsequent reduction to 37.5 µg (11 µg/kg/day) [9]. The tablet should be crushed and suspended in a few ml of milk or water. Concomitant intake of soya, iron, calcium, fiber should be avoided [2]. Written information and education should be provided focusing on etiology, need for early and regular treatment and regular follow-ups. Pharmaceutically produced L-T4 liquid can also be used [4]. The dose should be adjusted to ensure normal growth and development aiming for low normal TSH (0.5-2.0 mIU/L) and fT4 in upper half of reference range in the first 3 years of life [2,4]. The aim is to normalize T4 within 2 weeks and TSH within 1 month [4,5].

**Iodine**

Iodide supplementation with/without thyroxine may be useful in NIS defect and residual enzyme activity. Iodide intake is beneficial in maintaining euthyroid status in Pendred syndrome and in DUOX2 mutation. Lugol’s Iodine has been used as an alternative to L-T4 treatment in dehalogenase deficiency [1,8].

**Monitoring**

Clinical review with growth, (weight, length and head circumference) developmental and biochemical assessment is required in the first 3 years of life. Thyroid function is rechecked after 2-4 weeks, 1-2 monthly in the first 6 mo, 3-4 monthly between 6 months to 3 years of age and 6-12 monthly from 3 years of age till completion of growth and more frequently if there are concerns about compliance or with change in dose or source of medication. TFT should be checked at least 4 hours after the last dose and dose reduction should not be based on a single elevated fT4 levels. If fT4 does not increase into the upper half of the reference range by 2 weeks and/or TSH does not fall to <20 mU/L within 4 weeks, compliance, dose and method of administration should be checked [2]. Inadequate TSH suppression may be due to poor compliance, malabsorption, or increased degradation (anticonvulsants, large hemangiomas with high deiodinase activity). In persistent TSH elevation due to resetting of feedback or relative pituitary resistance, fT4 is used to titrate the dose. Overtreatment should be avoided as prolonged hyperthyroidism has been associated with craniosynostosis, poor concentration, behavioural problems, acceleration of growth and skeletal maturation.2.

**Re-evaluation**

Re-evaluation should be performed if initial diagnostic assessment was not done or did not suggest permanent CH,
initial TSH was <50 mU/L, especially in preterm/sick babies or if no TSH increase was noted after the newborn period, normal/slightly small gland was seen on USS with little or no uptake on scintigraphy. It is not required if dual imaging at diagnosis confirmed ectopy orathyreosis. L-T4 should be discontinued for 30 days after 3 years of age. After 30 days, if TSH is elevated to 10-20 mU/L and FT4 is low, the hypothyroidism is permanent and treatment should be resumed. Alternatively, dose may be reduced by 30-50% for 2-3 week. If the TSH is normal, the dose can be reduced further or stopped, with retesting after another 2-3 weeks. TFT should be repeated if any symptoms arise, he/she should not be lost to follow-up. If the results are inconclusive, careful follow-up and subsequent testing will be necessary [4].

Outcome

After introduction of neonatal screening, the prevalence of frank learning disability is minimal (1.4-4% attending special schools) [5]. Median IQ is reported to be normal due transplacental supply of maternal T4 and enhanced conversion to T3 offering neuro protection, however, mean IQ difference of 8-10.3 has been reported between patients and controls [5]. Problems with aggression, attention, memory and concentration, anxiety and less sociability have been reported. Some growth issues have been described, but if treatment is started early, there is unlikely to be any impact. Increased prevalence of hearing impairment (HI) compared with controls (9.5% versus 2.5%) is reported, and increased prevalence of hearing impairment have been described, but if treatment is started early, there is unlikely to be any impact. Increased prevalence of hearing impairment (HI) compared with controls (9.5% versus 2.5%) is reported, and ongoing hearing monitoring is essential. Cardiovascular health should be monitored as well. It is advisable to involve a pediatric endocrinologist in the initial stage of the evaluation, after which the pediatrician can follow up with support from the endocrinologist.

References

1. Beardsall K, Ogilvy Stuart AL (2004) Congenital hypothyroidism. Current Paediatrics 14: 422-429.
2. American Academy of Pediatrics (2006) Rose SR; Section on Endocrinology and Committee on Genetics, American Thyroid Association, Brown RS; Public Health Committee, Lawson Wilkins Pediatric Endo-

Your next submission with JuniperPublishers will reach you the below assets

- Quality Editorial service
- Swift Peer Review
- Reprints availability
- E-prints Service
- Manuscript Podcast for convenient understanding
- Global attainment for your research
- Manuscript accessibility in different formats (PdF, E-pub, Full Text, audio)
- Unceasing customer service

Track the below URL for one-step submission

http://juniperpublishers.com/online-submission.php
